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SMALL PUDDLES*

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THE first problem to confront a fledgling physician is the choice of habitat, or the arena in which theories are to be put to the test, the sphere that he hopes to influence, or, if you prefer your metaphors mixed, the waters on which the enriched bread of his services shall be cast. In wartime such a discussion might seem to be entirely without point, since all graduates of approved medical schools march directly into service uniforms with little or no choice as to settlement. And in a planned economy, even in the absence of war, of course the individual concerned is the last person to be consulted about such details.

Nevertheless, I choose to continue in this unpromising vein in the hope that we may salvage perhaps some historic value from a nostalgic review of the procedures of a simpler day. At least the effort is no more out of place than is a so-called "orator" who has been thrust without consultation from the dead-end silence of the vice-presidency to the uproar of this loud-spoken rostrum.

In the choice of field of practice, if the matter has not already been settled by some such accident as birth, the question of prime consideration is size — whether the community shall be large or small, whether provincial or metropolitan. Thirty years of service in an outlying district have prepared me to speak to some purpose from the preterurban, if not bucolic, point of view. Though this may be conceded, the intrusion of the personal touch, which I trust will be overlooked, necessitates a separate apology. I can speak with authority only of my own experience, but *ipso facto* the topic, "Small Puddles," I hasten to add, holds no pediatric connotation.

Fortunately, our own society has prepared statistics "as of February 15, 1942," which are appended to the *Directory of the Officers and Fellows*. Offhand the conclusion seems justified that the Secretary should assume the responsibility for the accuracy of these figures. Thus I would involve in their defense our able incumbent, Michael A. Tighe, whose gestures and aptitude for debate are beyond question more convincing than mine. Inasmuch as the current figures show in most instances an increase over the recapitulation of 1940, it is clear that war service had not yet depleted the ranks of membership and that the figures therefore are a reliable reflection of prewar conditions.

The Commonwealth of Massachusetts has been divided medically into eighteen districts, all but six of which are crowded into the eastern third of the state, where, as is obvious, the bulk of population dwells. Of 5074, the total number of active, resident fellows of the Massachusetts Medical Society as of the above date, 661 claimed Suffolk as their district. Norfolk sheltered 862, while the number in Middlesex South was 1005. That is to say, practically half the membership was enrolled in three districts alone, swimming either in or within easy jumping distance of the major puddle, Boston. There can be little question therefore that a great many incipient practitioners have preferred to risk the anonymity of being just another frog in a large and crowded puddle. This observation is further verified by the 2.4 per cent increase in Middlesex South during the past two years, which is more than twice that of Hampden (1.1 per cent) and almost twice as much as Norfolk's (1.6 per cent). The large Worcester puddle increased even more, 4.4 per cent, which should discourage further additions. The remarkable increase of 14.7 per cent in Barnstable may easily be explained by the establishment of Camp Edwards on the Cape. At any rate, there would seem to be no further room there for expansion. Of necessity, then, at least half the new men must look for placement in the small

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puddles. The heaviest agglutination of frogs was found to be as follows:

Middlesex South	1005
Norfolk	862
Suffolk	661
Worcester	425
Hampden	341
Total	3294

This merely substantiates the well-known fact that metropolitan centers seem to exert a strong attraction for numbers of individuals in all walks of life, including the bypaths of medicine. Some of them doubtless take comfort in the presence of a multitude of neighbors. The big city offers a challenge to others, particularly those who have been reared in less sophisticated centers. Small-town boys—and girls—have always seemed to like to prove that they can make good in the major leagues.

Still others find themselves metropolitans by accident. Paul White is one of the group which can qualify by the accident of birth. He was born in one of Boston's suburbs to grace the maturity of an honorable and capable practitioner of medicine whom it was my privilege to visit as a medical student. Only recently we have learned through a pleasing stroke of notoriety by what a narrow margin he avoided the tragic accident of serving a life term in the Tower of London instead of in the Bulfinch Building with such credit.[1] If Cornelia Skinner's mother had been less gifted, her daughter's smuggled measles might have altered history, even though they did not permanently change the damsel in distress.

I am at a loss, however, to explain the decision of a lovable Al Hornor who transplanted his sunny smile out of the Deep South into the bleak Back Bay so successfully that his happy accent is still unimpaired after thirty years of exposure to the harsh east wind that sweeps up Boston Harbor. I believe it was clinched by the power of the scientific spirit that impelled him to continue the pursuit of knowledge at the fountainhead. No man may question this, the best of reasons for settling in a puddle that seemed to be overcrowded. In the waters of science there is always room for talent and for devotion.

But I have seen, and so have you, not a few truly pathetic figures haunting the purlieus of the large metropolitan hospitals in the vain hope of a recognition that cannot come to all. Many of these misguided creatures could have been happy and respected frogs if they had shifted to smaller puddles before it was too late, or, better, had chosen wisely in the first place.

The accident of medical heritage no doubt is a factor in deciding many settlements, but no more so in rural than in urban localities. Nor is there always assurance that a medical son will elect to enter practice with his father. Not seldom he has preferred to strike out for himself, though the majority of such associations seem to be mutually appreciated. I have discovered that this factor has influenced 15 per cent of the fellow-occupants of our local puddle. Perhaps this is a fair average figure for all communities, but I have no available evidence to prove it either way. It is of interest rather than significance worthy of further consideration.

The less frequented waters in remoter regions of the Commonwealth were chosen in descending sequence thus:

Berkshire	134
Worcester North	102
Bristol North	75
Hampshire	73
Barnstable	61
Franklin	48
Total	493

It is somewhat startling to realize that all the frogs that inhabit the five least populous districts outnumber the total in the Hampden district by only 18 and that Hampden, in turn, stands only fifth in density of frog-units. Here, then, should be found *Lebensraum*, or better, room to swim in peace.

Passing from general considerations to particulars, or from ponds, let us say, to the study of the puddles in question, the Worcester district leads in number with forty-three, eleven of which are unoccupied by frogs. At the other extreme stands Suffolk, with only seven puddles and not one cipher among them. For contrast, the extremes in both occupied and unoccupied puddles have been grouped as follows:

NUMBER OF PUDDLES

MOST		LEAST	
Worcester	43	Middlesex South	13
Norfolk	36	Franklin	13
Plymouth	32	Middlesex East	12
Barnstable	30	Bristol North	7
Essex South	24	Suffolk	7

EMPTY PUDDLES

MOST		LEAST	
Berkshire	21	Essex North	1
Franklin	17	Essex South	1
Hampshire	12	Middlesex East	1
Worcester	11	Norfolk South	0
Hampden	9	Suffolk	0

It would appear that the Berkshire, Franklin and Hampshire districts offer more open expanses

of frogless water than all others, the westernmost district in particular, for in Berkshire, the empties outnumber the encumbered puddles by twenty-one to sixteen. Nor should Worcester be overlooked, with eleven vacancies. At least that was the picture in 1942. The fact should be borne in mind for future discounting, that there has been a large industrial expansion in various parts of the State that may vitiate these findings. Only the future will provide the answers to such questions as to how much of the war work can be salvaged, and whether or not physicians will be drafted where they are needed without the privilege of choice.

It might be kind, before the rush of nineteen-forty-niners sets in for the gold-bearing hills, to point out the unvarnished truth about these ghost-town puddles. With a barrier of ice and snow such as has but recently melted, the hill towns can challenge the most rugged individuals and put them to the test. Some few frogs before this have given up the fight, as others doubtless will in due time, because they could not sustain themselves and their families under such conditions. What is more to the point, they could not subsist on scenery alone.

But for some years now young men have not felt that they were called on to bury themselves, as the quaint phrase put it, when practice in the country was proposed. A. Warren Stearns, as dean of Tufts College Medical School, was one of the first to do something practical about stemming the tidal wave of specialism that had dangerously thinned the ranks of family doctors in the less populated districts. The scholarships that he was instrumental in raising still make it possible to nullify the prediction that Richard Cabot uttered with such finality a quarter of a century ago, that the general practitioner of medicine would soon be entirely extinct.

"As I go into towns like Bedford," he wrote in answer to my query, "which had not had a doctor for many years, and find the place that Dr. Lord has made for himself, I feel happily justified in what we have tried to do. And so I might go on, with Dr. Cole in Westford and Dr. Lewis in Groton, perhaps multiplying these several hundred times." "The people speak gratefully to me," he added, "for what we have done for the towns."

The towns, in fact, are no longer isolated as a result of modern contacts, tangible or air borne. And even tangibles promise to become air borne when a helicopter shall transport each practitioner, or television shall bring the image of the patient's ailing tongue with no expenditure of effort at all. There should be ample opportunity in those halcyon days ahead to enjoy the sunsets behind Mount Wachusett or a ski run to the summit of Greylock between calls.

As a matter of fact, there has always been time for frogs with receptive eyes to observe for themselves the manifestations of nature no matter where they are stationed. Even Roger Babson, the urbanite, has made a business of collecting sunsets. One of his choicest was observed from a hotel window in the heart of New York City. Again, I am sure that you too would have been thrilled, as I was, at the sight of that handsome but elusive duck, the redhead, taking refuge with a group of mallards in a wintry puddle in the Fenway within a stone's throw of Brookline Village. At least there could be no doubt of the reaction enjoyed by a fellow-practitioner when I pointed out for him the snowy crest of a great American egret across the back water of the Ox-Bow on our Connecticut River not so long ago. He had traversed the length of the State, but the heron had flown the long miles north from the Everglades of Florida.

And human nature, the never-ending source of wonderment and study, is universally available, in puddles large or small. Geographical considerations are not paramount in such studies, nor, in fact, in the full enjoyment of life when viewed with understanding. Lin Yutang,[2] for example, maintains that the West still has much to learn from China in such matters. "What the modern world needs," he wrote, "is not more intellectual brilliance, but more life wisdom." Not without point he added, "The truest test of a civilization is not how you are able to conquer and to kill, but how you can get the greatest kick out of life."

From a small puddle it is but a question of minutes rather than hours to get down to earth for a profitable communion with nature, whether in pursuit of birds or birdies, as individual taste may dictate. In like manner the greater intimacy of the smaller community brings human beings more readily within range. They are not so apt to remain lay figures to be laid aside at the close of day, or the records of their troubles merely to be filed with other interesting data at the end of the service. There indeed is the rub. They have feelings that must be respected — and the spotlight of publicity searches out every action of the upstart in their midst.

Conversely, when knotty problems have been solved, and the perishing have been rescued — the appreciation is prompt and lasting. The resulting relation of affectionate trust and respect outweighs many times the larger financial rewards that are said to accrue in the more ambitious puddles. After thirty years of such experience, I can

underline this last as the most convincing argument in favor of practice in small puddles.

It is more feasible, likewise, to share the public life of a small community. Such participation, though, may prove to be a liability. Indeed, a backward glance over the history of the particular puddle that I call home reveals the downfall of several frogs who played at politics. These catastrophes merely serve to re-emphasize the truth of the assertion that Medicine is a jealous mistress, and intolerant of rivals. A physician, I believe, even in a small town, should not limit his usefulness by taking sides except in matters of principle. There are too many caesars already without us to tend to such affairs. Nevertheless, it is still true that a willing frog may serve to good purpose by taking his share in the life of all who inhabit his own small puddle. During a lifetime spent in such surroundings, unknown talents may be discovered that never would have seen the light of day, and opportunities will multiply to study uncharted problems.

Jenner, for one, often has been held up as an example of what an alert mind can accomplish in a small community. Horace Wells, of Hartford, is another, and Austin Flint, of Northampton and Buffalo. Then there is Rafinesque of Kentucky, who anticipated Darwin's observations on deviations and mutations by twenty years. For a change, let me cite the case of Karl, the son of Nils, of oldtime Sweden.[3] He hewed for himself the Latin surname of Linnaeus out of his family's linden tree and won fame for the name by patiently classifying the number of stamens and pistils of flowers that bloom in the spring, while medieval herbalists still floundered. But when it came to taking a wife, the country boy returned to his small puddle for thrifty Sara Moroea, who is said to have thrashed her daughter, spoiled her son and urged her husband to quit meddling with science and turn to earning fat fees as a physician at the Court of Gustavus the Third.

But what of "ziss frog," as Franz Pfaff used to say, the one whose motives should be most familiar? Once he had to choose like other beginners between a mighty puddle and a small one. Continued research in bacteriology with A. I. Kendall was worthy of most serious consideration. And the academic life with regulated hours held a strong appeal. Yet the lure of a vast metropolis was more easily denied. Anticipation of new scenes soon faded under the potent charms of one small puddle that lay within the broad curve of the "Long River" and mirrored the form of the familiar mountain. Prospective pursuit of fractious anaerobes yielded to the call of native flora and fauna. In other words, the tap roots and family ties proved too strong to be torn loose. So one more decision must be credited to natal implantation.

Hear ye, then — ye who are about to enter upon the practice of medicine. Do not abandon hope, but elect instead to agitate some small puddle just as this stiff-jointed frog chose to do. It is certain that he would do so again if the choice, by some magic of Merlin, ever should recur.

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PRACTICAL CONSIDERATIONS IN THE THERAPEUTIC USE OF BLOOD DERIVATIVES*

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WITH the increasing availability and use of liquid, frozen and dried human citrated plasma and of human serum albumin has come the realization that these blood derivatives are frequently not merely substitutes for whole blood but therapeutic agents in their own right, each with its own indications and contraindications and each presenting its own practical problems. In order to prevent the misuse of any of these derivatives and their consequent discredit, it is thought desirable to review certain of these practical considerations.

SERUM ALBUMIN

The most recent of these blood derivatives—namely human serum albumin—perhaps deserves the first attention, because certain misconceptions concerning its use have already arisen. Albumin should not be considered a substitute for plasma, and certainly not for whole blood. It represents a relatively stable concentrated solution of that fraction of the plasma proteins mainly responsible for the maintenance of the colloid osmotic pressure of the blood, and its chief advantages exist where storage or transportation space is at a premium. Thus, it may be of value in some military situations. However, in medical establishments of moderate size, ashore or afloat, where space is available for the storage of dried plasma, there are few, if any, indications for the use of serum albumin. Human serum albumin, therefore, will not be made available for routine use in such installations.

The chief dangers in the use of human serum albumin arise from the facts that it represents but one of the serum proteins, and that it is extremely hypertonic and supplies practically none of the fluid that may be needed in the treatment of traumatic shock, burns or hemorrhage. Woodruff and Gibson[1] have already reported the case of a burned patient treated with albumin to a point where the albumin-globulin ratio went to 6.7-0.7 and the prothrombin time was prolonged. Inasmuch as complement and antibodies are also contained within the globulin fraction, it is evident that this sort of situation is fraught with dangerous possibilities. In burns, citrated plasma should follow albumin as soon as possible, and arrangements should be made to transport the patient promptly to an area where this is feasible or to transport plasma to the patient.

In traumatic shock, albumin must be considered solely as an emergency first-aid measure. The precautions (included in every package of serum albumin) outlined by the Committee on Clinical Evaluation of Human Albumin, relative to increasing hemorrhage, to aggravating existing dehydration, to increasing apparent anemia, to potential pulmonary edema, to the limit of dosage and to the stability of the solution, must be borne constantly in mind.

If it is desired to administer a hypertonic blood derivative, as for example in hypoproteinemia, or in certain burned patients, concentrated plasma may be preferable to albumin. The former can be administered very simply with the standard Army-Navy package of dried plasma, as described below.

The concentrated solution of human serum albumin is quite stable at the moderate temperatures encountered in the temperate zone. The package, however, must not be kept at freezing temperatures or at temperatures exceeding 50°C. (122°F.). At temperatures approaching the latter level, turbidity and gel formation may take place, and on long storage at ordinary temperatures a small amount of fine flocculation has occasionally been observed. So long as these reactions are not excessive, they do not affect the efficacy or toxicity of the product. However, as a precautionary measure should excessive flocculation occur, a small filter has now been included in the standard Army-Navy package of normal human serum albumin (concentrated).

LIQUID PLASMA

It is quite evident, from the experience acquired to date, that plasma, when prepared by a *closed method with scrupulously aseptic technic*, may be preserved in the liquid state at room temperature in a medical establishment in the temperate zone for at least as long as fourteen months. Over two thousand administrations of plasma

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prepared and preserved in this manner by the Plasma Department of the Naval Medical School have been analyzed, with a reaction rate of approximately 1 per cent. The permissible temperature range of preservation probably lies between 15 and 30° C. (59 and 86° F.). Below this range excessive fibrin precipitation may occur, and above this range protein denaturation occurs rapidly. Although a small amount of fibrin precipitation is almost inevitable when plasma is preserved in the liquid state, this does not affect its efficacy or safety. It is imperative, however, that a filter be used in the intravenous set when the plasma is administered. Numerous types of filters have been devised for this purpose, and most of them are satisfactory. Glass cloth and stainless steel mesh, alone or in combination with glass beads or latex airfoam, when properly prepared and assembled, have been used successfully at the National Naval Medical Center.

Frozen Plasma

When liquid plasma, prepared by the same closed and scrupulous technic, is frozen within twenty-four hours after preparation at a temperature below -20°C., it may be preserved indefinitely, if stored below -15° C., without loss of any of the thermolabile constituents, such as prothrombin, complement and antihemorrhagic factor[2] ("plasma thromboplastin"). Thawing must be done in a water bath at body temperature (37° C.) with occasional shaking, and should not take longer than thirty minutes per bottle of plasma. It should never be attempted in an incubator. Thawing at a temperature below this level produces a massive fibrin precipitate, most of which goes into solution again if the plasma is promptly placed in a water bath at 37° C. A filter is not absolutely necessary if the frozen plasma is thawed properly, maintained at room temperature and administered within two or three weeks after thawing. However, inclusion of the filter in the intravenous set is a wise additional safeguard.

The plasma should be frozen in a near-upright position, a few bottles at a time, so that each bottle will freeze in less than three hours. A refrigerator containing a fan for circulating air over the cooling coils greatly accelerates the freezing. The plasma should then be stored in the horizontal position so that accidental thawing can be quickly detected. Precautions should be taken against discontinuance of the power supply to the refrigerator, and against too frequent opening of the refrigerator doors. It is advisable to have an available source of solid carbon dioxide (dry ice), should the power be discontinued and in the event of mechanical breakdown. An internal-combustion engine can also be used in this exigency to run the compressor for the refrigerator. An alarm system should be installed in the refrigerator and adjusted to give a suitable signal when the temperature goes above -15° C.

Once accidental thawing has occurred, it is absolutely imperative that a good filter be used in the final administration set. There are three methods of handling this situation, none of which, however, prevents a certain amount of fibrin precipitation. If the refrigerator is operating, the plasma may be refrozen immediately, or thawing may be allowed to continue at 37° C. and the plasma stored as liquid plasma from that time on, or it may be then refrozen. In any event, much of the prothrombin and complement will be lost, and this advantage of preservation in the frozen state will therefore no longer exist.

Dried Plasma

The standard Army-Navy package of dried plasma can survive a wider range of temperature variation without denaturing or precipitating protein than can any of the other blood derivatives or forms of preservation. The package should not be permitted to freeze, nor should it be permitted to stand for any length of time above 55° C. (131° F.). If the plasma has recently been stored above 37° C. (98° F.), care must be taken to be absolutely certain that at the time of restoration the temperature of the water is not above 37° C., for in this event the proteins of the plasma may be either denatured or precipitated and untoward reactions may ensue. If the medical officer is in doubt concerning the maximum temperature to which the package has been subjected, he should be guided by the solubility time on restoration and the gross appearance after restoration. The solubility time should be less than three minutes with a small amount of shaking, and the gross appearance should be that of an opalescent or turbid solution without gross sediment, precipitation or gel formation.

Three hundred cubic centimeters of twice-concentrated plasma may be easily obtained using two standard Army-Navy packages of dried plasma. One bottle of plasma should be restored according to directions and used instead of the bottle of distilled water to restore the second bottle of plasma. In this manner the dried equivalent of 600 cc. of human citrated plasma will be dissolved in 300 cc. of distilled water.

Every medical officer who is expected to use plasma should familiarize himself with the directions of the restoration and administration of the standard Army-Navy package of dried plasma and follow them explicitly. The length of time

required to set up this package is a significant factor in the prognosis of a wounded patient. With a small amount of experience, the package can be opened, restored and prepared for administration in less than five minutes. The commonest error encountered is releasing the vacuum in the plasma bottle with the double-ended needle before this needle has been inserted in the water bottle. It should always be inserted in the water bottle before insertion in the plasma bottle.

The Subcommittee on Blood Substitutes of the National Research Council has recently recommended, and the Division of Biologics Control of the National Institute of Health has approved, the substitution of 0.1 per cent citric acid for the 0.1 per cent sodium chloride in the pyrogen-free distilled water used at present to restore dried plasma. This substitution was recommended because of the observation that with the present methods of vacuum drying, restoration with a non-buffered neutral diluent produces an alkaline plasma.[3] This alkalinity is relatively detrimental to such labile plasma constituents as prothrombin and complement. Restoration with a slightly acidified water will prevent destruction of these labile factors after reconstitution.[2, 3] This change has now been made in the standard Army-Navy package of dried plasma.

It has been believed for some time that it would be extremely desirable to include more plasma in the standard package. The majority of patients are now receiving an initial dosage approximating 500 cc., especially in the war zones. Accordingly, the package has been redesigned so that the amount contained will approach this figure.

In recent months, several communications[4-6] have appeared in the medical literature concerning the alleged toxicity of plasma. A review of the results obtained from the plasma prepared at the Naval Medical School, and of the entire literature, has led us to the conclusion that the dangers from *properly prepared pooled* human plasma are practically nil. Thalhimer[7] arrives at the same conclusion. Neither preliminary cross-matching nor skin-testing, both of which have been suggested by these critics, are, in our opinion, necessary. We have never observed a true hemolytic reaction following the use of pooled plasma, nor are we aware that one has been reported. Localized or generalized urticaria has followed the use of plasma in approximately 1 per cent of cases in our experience. This has invariably been easily controlled with subcutaneous adrenalin. The incidence of such reactions may be diminished but not eliminated completely by the use of fasting donors. If the untoward reaction rate from the administration of plasma exceeds 2 per cent, one should be highly critical of the preparation of the equipment and the methods used in collecting blood and in aspirating, pooling and administering the plasma.

Dosage

The experience in this war with the use of blood derivatives in the prevention and treatment of shock due to trauma or burns has confirmed, beyond all question, the wisdom of administering an adequate amount early, preferably before the onset of symptoms of shock. In this, as in other military situations, error on the side of "too little and too late" is far more dangerous than "too much and too early." The possibility of the occurrence of irreversible physiologic and anatomic changes and death is directly proportional to the interval between injury and infusion with a blood derivative, and inversely proportional to the dosage used. There is also a direct relation between the amount of blood derivative required and the elapsed time after injury. Bearing these principles in mind will both decrease mortality and prevent waste of these precious materials.

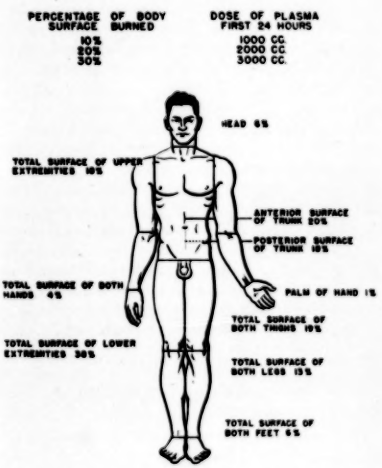
PERCENTAGE OF BODY SURFACE BURNED
DOSE OF PLASMA FIRST 24 HOURS
10% 1000 CC.
20% 2000 CC.
30% 3000 CC.
HEAD 6%
TOTAL SURFACE OF UPPER EXTREMITIES 10%
ANTERIOR SURFACE OF TRUNK 20%
POSTERIOR SURFACE OF TRUNK 18%
TOTAL SURFACE OF BOTH HANDS 5%
PALM OF HAND 1%
TOTAL SURFACE OF BOTH THIGHS 19%
TOTAL SURFACE OF LOWER EXTREMITIES 36%
TOTAL SURFACE OF BOTH LEGS 13%
TOTAL SURFACE OF BOTH FEET 5%

FIGURE 1. *The Adjustment of Dosage of Plasma in Burns according to Percentage of Body Surface Burned (modified from Berkow[8]).*

Under the conditions imposed by modern warfare, the initial dosage of plasma or albumin must rest wholly on the judgment of the surgeon. Five hundred to 1000 cc. of plasma or 25 to 50 gm. of albumin is an advisable initial dose following a

severe injury or burn. An attempt should be made to utilize the laboratory aids of red-cell count, hemoglobin level, hematocrit and total protein content for the regulation of subsequent dosage, but the medical officer will frequently be forced to rely solely on the clinical response of the patient, including pulse and blood-pressure readings. In burns, a rough but useful rule for estimating the first day's dosage is to administer 100 cc. of plasma for each 1 per cent of the body surface burned, up to a maximum of 4000 or 5000 cc. Estimation of the area involved should be by Berkow's chart[8] (Fig. 1). The knowledge that the palmar surface of one hand represents approximately 1 per cent of the total body surface is often very useful. When hemoconcentration has supervened, it has been advised[9] that 100 cc. of plasma be given for every point the hematocrit is above 45.*

The use of whole-blood transfusions supplementing plasma or albumin may be of extreme importance in determining the prognosis of a wounded patient. The need for red cells may be masked initially by hemoconcentration. In burns, moderate anemia is prone to develop and is affected apparently only by blood transfusions.

The rate of administration of these derivatives should not exceed 10 cc. per minute for plasma or 5 cc. per minute for albumin unless clinical shock is present. In that eventuality it may be advisable to administer the material with double this speed.

Intravenous Tubing

In all medical establishments that prepare rubber tubing and glassware for drawing blood and administering blood, plasma, albumin or other solutions, the personnel detailed to such preparation should be thoroughly conversant with the so-called "pyrogen-free" technic.[11, 12] Unless such technic has been scrupulously followed, it is impossible to evaluate properly untoward reactions following intravenous infusions.

*These rules were tested at the Boston City Hospital following the Cocoanut Grove disaster by Dr. C. C. Lund, Dr. F. H. L. Taylor and their co-workers[10] and found to be helpful.

Summary

Certain practical considerations relative to the use, abuse and storage of human serum albumin (concentrated) and liquid, frozen and dried plasma are briefly discussed. It is advised that medical officers familiarize themselves with these matters, lest an inordinate number of untoward reactions following the use of blood derivatives, and unnecessary waste of these precious materials, be permitted to occur.

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BIOPSY OF THE PROSTATE WITH THE SILVERMAN NEEDLE*

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THE frequency with which carcinoma of the prostate occurs in elderly men has been recognized for a long time, yet the diagnosis is seldom made until the symptoms of urinary retention occur. For example, Rich[1] reported that in 292 consecutive autopsies in men over fifty 14 per cent showed carcinoma of the prostate, and in 65 per cent of these cases the diagnosis of carcinoma was not made during life. Since these cases were reported from the Johns Hopkins Hospital, it is obvious that, for the country as a whole, the percentage of unrecognized cases must greatly exceed this figure, especially in the older age groups, where the incidence of carcinoma of the prostate climbs rapidly to the astounding figure of 37 per cent. Because of the importance of this problem and because of one's inability to make the diagnosis by rectal palpation in early cases, and in a not inconsiderable number of more or less advanced cases, we began a year and a half ago to investigate seriously the possibility of prostatic biopsy. Although from time to time most urologists have removed pieces of prostatic tissue for microscopic examination, few have realized the simplicity or value of routine biopsy with the Silverman needle. For this reason it has seemed worth while to present our results in 36 cases.

There are four ways of removing prostatic tissue for biopsy: by perineal exposure, by transurethral resection, by aspiration biopsy and by punch biopsy. Of these methods, the only one that can be followed as an office procedure and that removes an amount of tissue sufficient to be studied by the usual pathological technic is the punch biopsy. For this reason we have carried out punch biopsies, using the Silverman needle. Although this is only one of several instruments designed for this purpose, it has seemed to us, from a purely theoretical consideration, to be the most satisfactory. We have had no experience with other methods of punch biopsy.

We admit that the best method is perineal exposure and biopsy under direct vision. This method, however, has one great drawback: it requires general anesthesia and about a week of hospitalization. It is ideal in those cases where perineal prostatectomy is indicated, since it can be carried out as part of the operation to determine whether a partial or a total prostatectomy is required. However, in those cases in which perineal prostatectomy is not indicated, the magnitude of the procedure often results either in refusal of the patient to submit to the biopsy or in failure of the surgeon to recommend it. The removal of tissue for biopsy by transurethral resection has the same disadvantage in that it requires general anesthesia and at least some hospitalization. Another objection to this method is that the tissue removed must necessarily come from near the urethra, whereas the prostatic cancer most frequently originates near the capsule, where it cannot be reached by the resecting loop. Cases of carcinoma of the prostate are frequently seen in which the pathologist is unable to find evidence of malignancy in the tissue removed by transurethral resection. In this series there was 1 case in which 4 gm. of tissue had been removed by transurethral resection, with no evidence of malignancy having been found. However, since rectal examination of the prostate indicated a moderately advanced carcinoma, a biopsy with the Silverman needle was subsequently carried out. This showed malignancy, thereby establishing the diagnosis.

Although Ferguson[2] has reported excellent results with aspiration biopsy of the prostate and was able to remove tissue in from 78 to 86 per cent of his cases, we have not found this method satisfactory, for two reasons. In the first place, we have found it difficult to remove any tissue. In the second place, no pathologist who has not had extensive experience with the examination of material removed by aspiration biopsy is able to make a diagnosis, since the slide consists of nothing more than a smear of cells not unlike a blood smear. All the normal histologic arrangement is lost, and it is quite impossible to study the tissue or to grade the malignancy. On the other hand, although the amount of tissue removed by punch biopsy is small, it is large enough to fix and cut in the usual way. Thus it is possible for any pathologist not only to make the diagnosis, but also to make an estimate of the degree of malignancy and radiosensitivity.

The needle described in 1938 by Silverman[3] has been used extensively by him and others to remove tissue from the liver, lungs and other organs, but has not, so far as we know, been used for prostatic biopsy. It is made in two lengths,

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and for this work the longer (3⅜-inch) needle is necessary. The instrument consists of two parts: an outer 14-gauge needle, or cannula, and an inner needle, which is longer than the outer sheath and is split longitudinally from point to hub. The principle of operation is simple. The cannula is inserted up to, but not into, the suspected tumor.

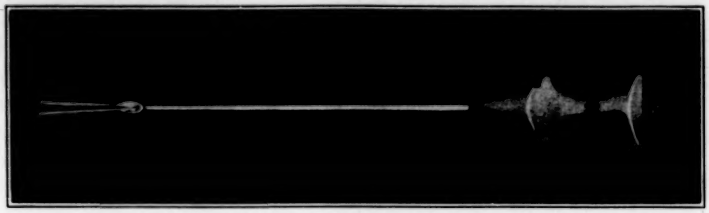

FIGURE 1. *The Silverman Needle.*

It is then held stationary while the inner needle is inserted through the outer one and into the mass from which a specimen is to be obtained. The split needle engages a section of the mass and holds it between its prongs. The outer cannula is then advanced over the prongs so as to cut off the piece of tissue and the entire instrument is removed. If this maneuver is properly executed a piece of tissue measuring 1 by 10 mm. is obtained. Since the piece is small it should be placed immediately on a piece of filter paper, which should be put in the fixing solution as soon as the operation has been completed.

In performing a biopsy on the prostate gland the patient is put in the extreme lithotomy position, the perineum is infiltrated with novocain, and, guided by a finger in the rectum, the needle is inserted to the desired spot. The accuracy with which this can be done depends entirely on how easily the prostate can be palpated, but unless the patient is excessively fat and nonco-operative this is not difficult. The only pain of which the patient complains is from the finger in the rectum. The biopsy can be accomplished without any help, but it is convenient to have an assistant hold the inner needle steady while the outer cannula is advanced so that several pieces may be cut without removing the finger from the rectum. None of our patients have had any reaction, and we have not hesitated to carry out the procedure on those who are ambulatory. In 3 cases we have inserted the needle too far and it has entered the bladder. In these patients there was slight hematuria but no other complications occurred.

In considering the value of prostatic biopsy, it must be realized that only positive reports are of real significance. A negative report merely means that the pieces of tissue removed show no malignancy, although other parts of the gland may be malignant. However, if four or more pieces of tissue, each measuring 1 by 10 mm., are obtained from every suspected prostate, an earlier diagnosis is possible than if one relies, as in the past, on simple rectal examination. In this series we have not succeeded in finding an early case of carcinoma of the prostate suitable for total removal, but this is, we believe, more a criticism of the medical profession as a whole than of the method.

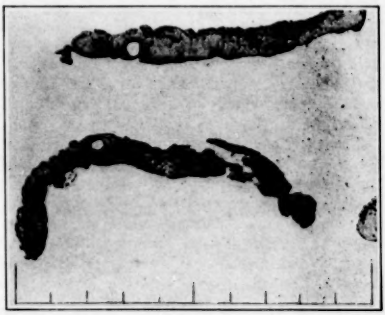

FIGURE 2. *Low-Power View of Specimens.*

These were obtained from a patient with benign hypertrophy of the prostate; the photograph shows their entire size. The markings on the lower edge of the cut represent one centimeter divided into millimeters. (Alcohol-formalin and celloidin technic; phloxine and methylene blue stain; magnification, × 18.)

Seldom does one see early questionable cases of carcinoma of the prostate, but it seems likely that if it were generally realized that a simple technic exists by which the prostate gland can be biopsied, many more early cases would be referred to the urologist for diagnosis. In some cases, at

least, a positive biopsy would be obtained, a successful radical prostatectomy could be carried out, and a life would be saved.

However, aside from the question of early diagnosis, biopsy of the prostate has been of real

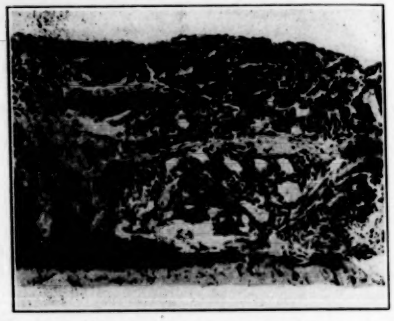

FIGURE 3. *Low-Power View of a Specimen.*

This was from a patient with a carcinoma of the prostate; it shows extensive infiltration of the stroma by moderately anaplastic, hyperchromatic tumor cells. (Zenker and paraffin technic; phloxine and methylene blue stain; magnification, × 160.)

value in a number of cases. For example, we have used this method to confirm the diagnosis of carcinoma before doing a bilateral orchidectomy. To be sure, in most of these cases the diagnosis can easily be made by rectal examination, but it seems desirable nevertheless to confirm it with a pathological diagnosis. In a recent case the patient returned to the Lynn Hospital six years after a transurethral resection. The original slides had been reported as showing carcinoma, but they were not available for re-examination. Cystoscopic examination showed no evidence of recurrence, and although the prostate felt hard on rectal examination, it was not enlarged. We were unable to make a positive diagnosis, and because of the long time that had elapsed since the operation, it seemed that the original diagnosis might have been incorrect. However, it was easily confirmed by biopsy, and a bilateral orchidectomy was done. In the cases of carcinoma of the prostate treated by orchidectomy we hope to repeat the biopsy at a later date, and by comparing the two slides to learn something about the histologic changes that occur in the malignant gland following removal of the testicles. From the research point of view, this appears to be an ideal way of studying the effect of various hormones on the gland. Biopsy is also of some value in these cases in giving a prognosis and in enabling one to decide whether x-ray treatment is indicated, since some idea of the degree of malignancy and radiosensitivity can be obtained.

We have also found biopsy of value in planning the type of operation in cases in which there has been some doubt concerning the diagnosis, and in certain cases even negative evidence has been helpful. The greatest value of prostatic biopsy in this series, however, has been in confirming the diagnosis of carcinoma of the prostate in suspicious but not definitely proved cases in which, because of the lack of urinary symptoms, no operation was indicated. The fourth case of this series is a good demonstration of the value in this type of case. The patient had an unexplained edema of the left leg which his surgeon thought might be due to

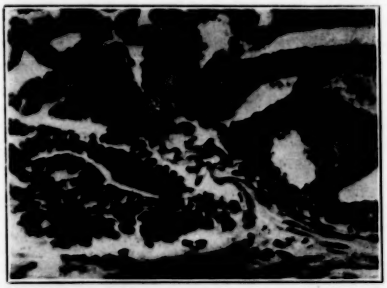

FIGURE 4. *High-Power View of an Area of the Section Shown in Figure 3 (magnification, × 450).*

metastases from a malignant prostate. We made a careful rectal examination and reported that we did not think the patient had carcinoma of the prostate. However, since we were interested in seeing what could be accomplished with the needle, we did a biopsy on the prostate gland. Much to our surprise, the removed tissue showed carcinoma. The subsequent course of this case has proved the diagnosis to be correct. There was an interesting medicolegal angle to this case, since the patient later claimed that his disability resulted from an accident. The prostatic biopsy was of considerable importance to the insurance company in proving that this was not so. In several other cases the biopsy was of distinct value in confirming the diagnosis of carcinoma where it had been suspected from the x-ray findings or other evidence but could not be proved by rectal examination.

We have carried out biopsies in a series of 36 cases, with the following results. Sixteen cases

were reported as carcinoma. The diagnosis in all these cases has been proved to be correct, either by the examination of tissue removed at operation or by the subsequent course. In 17 cases the tissue showed no evidence of carcinoma. Five of these cases were not operated on, and in 10 cases the diagnosis was proved correct by operation. In 2 of the 17 cases the diagnosis was incorrect, since the patient had carcinoma of the prostate. One of these cases had a second biopsy that was positive. In 3 cases we failed to remove a satisfactory amount of prostatic tissue for examination. These cases need further comment. We had no difficulty in removing tissue from the first 13 cases in which we attempted a biopsy. However, after the needle was broken in an attempt to biopsy a bone tumor, we commenced to experience difficulties. We subsequently discovered that these needles are all made by hand and without definite specifications, so that no two are alike. A small variation in their construction or the type of steel used makes a considerable difference in the ease with which the tissue can be removed. The manufacturer has been co-operating with us and this technical difficulty seems to have been corrected, so that in the future we expect to be able to remove adequate amounts of tissue in every case. It has been our experience that in a hard, malignant gland there is never any difficulty in removing an adequate amount of tissue. Since this is the type of gland one is most anxious to biopsy and the most difficult to handle by aspiration biopsy, the relatively few failures do not detract greatly from the value of the needle.

Summary

The Silverman needle was used to biopsy the prostate gland in 36 cases, with satisfactory results in 86 per cent. As a means of removing tissue this method is safe and simple, and is applicable to ambulatory patients. It is of value not only as an aid to the early diagnosis in carcinoma of the prostate, but also in establishing or confirming the diagnosis.

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MEDICAL PROGRESS

SKIN CHANGES OF NUTRITIONAL ORIGIN*

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NUTRITION is becoming an increasingly complex and important subject. Almost every vitamin deficiency has been produced experimentally in human beings in pure form and the resultant clinical manifestations have been carefully studied. Experimental specific amino acid deficiencies in human beings[1-3] have likewise been produced. The results of these definitive experiments indicate that there is often a considerable overlap in the clinical syndromes produced by each pure deficiency. Symptoms and signs commonly considered specifically diagnostic of certain deficiencies are beginning to assume new or additional meanings. Likewise, failure of a number of manifestations attributable to vitamin deficiencies to respond to the recommended therapy has emphasized anew that there are etiologic backgrounds for disease other than vitamin deficiencies.

There have been numerous reviews describing the clinical pictures of the various vitamin deficiencies. A novel and helpful approach to this general subject is to consider some one area of the body, describe its specific anatomy and function, and relate how vitamin deficiencies as well as other etiologic factors influence it. In last year's progress report the tongue changes seen in nutritional deficiencies were reviewed with that approach. The present review deals in a somewhat similar manner with a number of skin changes of nutritional origin. The subject is a pertinent one in view of the rapid advance in the use of vitamin therapy in the field of dermatology.[4-15]

The articles in the medical-progress series of 1941 have been published in book form (*Medical Progress Annual*, Volume III. 678 pp. Springfield, Illinois: Charles C Thomas Company, 1942. $5.00).

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Carotenemia and Carotenoderma

In spite of the widespread use of vitamin preparations during the last ten years, the scarcity of reports of untoward effects of excess vitamin in-

gestion indicates that these occur infrequently. In general this is true. There are, however, two significant exceptions. Hypervitaminosis D is one of these. This is a condition characterized by hypercalcemia with resultant metastatic deposition of calcium in various tissues, which at times leads to a fatal termination.[16-19] Massive doses of vitamin D, not ordinarily used clinically, have been primarily responsible. The other exception is carotenemia, which may result either from ingestion of an only moderate excess of carotene, whether as a medicinal preparation or in natural foods, or from impaired ability of the body to metabolize the amount of carotene present in a normal diet.

Hess and Myers[20] in 1919 were the first American writers to call attention to this condition. They proposed the term "carotenemia" for the yellowish pigmentation of the skin noted in persons consuming excess amounts of carrots and other vegetables. The condition had been known but not so well understood in Europe prior to that time. It was said to have been frequently observed in Germany during and after World War I because of the predominant vegetable diet utilized by the German people in those years.[21]

Numerous cases of carotenemia have been reported. The earlier literature has been thoroughly reviewed by Boeck and Yater,[22] Greene and Blackford[21] and Stannus.[23] A stimulating paper by two English investigators, Almond and Logan,[24] has recently aroused a renewed interest in carotenemia. Their paper is well worth reading. Because this subject is of wartime importance and has not been considered recently in an American review, a brief summary of the pertinent facts will be presented.

The yellow color seen clinically in carotenemia is not always due to carotene alone. Thirty or more pigments constitute the lipochrome or carotenoid group of pigments so widespread in natural foods, including plants and some species of animals.[25] Those of clinical interest are predominantly of a yellow shade; others vary from yellow to red.* The carotenoid (lipochrome) pigments are not to be confused with the green pigment chlorophyll also widely present in natural foods. Alpha-carotene, beta-carotene and gamma-carotene and cryptoxanthine (collectively or separately called carotene) are the four pigments with provitamin A activity. Pure beta-carotene is the standard reference material for the vitamin A unit, 0.0006 mg. being the equivalent of 1 international or *U.S.P.* unit of vitamin A. All the rest of the carotenoid pigments are physiologically inert in forming vitamin A, although they may have much to do with the yellow color in certain foods and may perhaps contribute to the yellow color of carotenemia in patients. Alpha-carotene, beta-carotene, gamma-carotene, cryptoxanthine and xanthophyll are the pigments most important in causing carotenemia in man.

For example, carotene is abundant in carrots, pumpkins, yellow squash, yellow turnips, sweet potatoes, parsnips, spinach, green or yellow beans, kale and oranges, as well as in butter and eggs; zeaxanthine is present in yellow corn and egg yolk; lycopene is a prominent lipochrome pigment in tomatoes and certain berries; xanthophyll is present in egg yolk and green vegetables and so forth. Although the yellow color is obvious in such foods as carrots or pumpkins, it should not be forgotten that the chlorophyll in green vegetables may mask equally great quantities of yellow pigment in other foods, for example spinach. Carrots, pumpkins, yellow squash, yellow turnips, parsnips, spinach, green and yellow beans, kale, oranges, eggs and papaya have been specifically recorded in the literature as being responsible for carotenemia.[26, 27]

Carotene (provitamin A) is absorbed in the intestinal tract, probably in the presence of adequate dietary fat and bile acids.[24] It is carried to the liver, where conversion to vitamin A takes place. Excess carotene is destroyed in the body or excreted in the sweat. Loss in the urine has been claimed.[20]

Because carotene is not the only yellow pigment involved in carotenemia, Boeck and Yater[22] suggest the name "xanthemia" for the condition of the serum due to lipochrome pigments, and "xanthosis" for the visible presence of these yellow pigments in the skin. In a similar sense Stannus[23] used "hyperlipochromemia" and "hyperlipochromodermia" as appropriate names for the condition of the serum and skin, respectively. Xanthosis cutis, aurantiasis cutis, carotenoid pigmentation, pseudoicterus, carotenosis cutis, xanthosis diabetica and carotenoderma are other synonyms.[21-30] "Carotenemia" is, however, the term most widely used in this country. It usually implies a yellow color of the skin as well as of the serum. However, much like latent jaundice, mild serum carotenemia may exist without a clinically detectable skin pigmentation, the diagnosis of carotenemia then being possible only by means of a test of the blood serum. "Carotenoderma" is a most descriptive term for the skin pigmentation resulting from carotenemia and deserves wider use than it now has.[30]

*Human beings may rarely show a clinically significant red pigmentation, especially of the serum and urine. Most notable have been the reports of anthocyaninemia and anthocyaninuria, due to excess ingestion of beets, which contain the red pigment anthocyanin. The red urine has been commonly confused with hematuria and hemoglobinuria.

The carotenoid group of pigments color the serum and fix themselves to the fat of the dermis and subcutaneous tissues, to which they impart the yellow tint. They are deposited in the horny layer (stratum corneum) of the epidermis and in the sebaceous glands.[24, 31] Edwards and Duntley[32] showed by means of spectrophotometric analysis of skin color in human beings that carotene is present in every normal skin and is one of the five basic pigments that determine the skin color of every living person. Clinically, therefore, carotenemia refers to the presence of an excess over normal of carotene in the skin and serum.

The ease with which the yellow pigmentation of the skin in carotenemia has been misdiagnosed as, or confused with, jaundice has been a major theme in the numerous papers on this subject. In most cases carotenemia results simply from excess use of foods rich in the carotenoid pigments. Individuals probably vary in the ease with which carotenemia develops, which is evidenced by the fact that many vegetarians do not develop it.[30] It is said to develop more readily in those who sweat profusely. Except for the yellow color produced, it appears to be harmless, even though present for months. It eventually disappears over several weeks to months when the carotene consumption is reduced. Carotenemia may readily appear when large doses of pure chemical carotene are used medicinally as a source of vitamin A.[33] Here, likewise, it is harmless and disappears slowly when the carotene dosage is reduced.

Carotenemia is frequent in diabetic patients. Boeck and Yater[22] found the blood carotene increased in 86 per cent of 100 such patients studied; however, only 10 per cent had a detectable yellow pigment in the skin. Stueck, Flaum and Ralli[34] report a study of 13 diabetic patients with clinical evidence of carotenemia. Other similar studies emphasizing this frequency in diabetic patients[35, 36] have been made. It is believed to be due both to the high lipochromic diet used and to the diminished conversion of carotene to vitamin A in the liver.[24] Because of the frequency of this condition in diabetic patients, the finding of carotenemia necessitates considering diabetes mellitus as a possible cause.[21]

Patients with kidney disease may manifest some degree of carotenemia, possibly owing to poor urinary excretion of this pigment; this is a point by no means agreed on. Boeck and Yater[22] noted xanthosis (carotenoderma) in 10 per cent and xanthemia in 100 per cent of their kidney cases. However, the pigmented element of the yellowish pallor noted in uremia may be due in part to retention of urinary chromogens that are oxidized in the exposed portions of the skin to the corresponding yellow pigments, the accompanying pallor being due to the anemia so frequent in uremia.[37]

The recent reports by Escamilla[38] and Mandelbaum et al.[39] confirm earlier observations[24, 40] that the yellowish color so frequently noted in myxedema is due to carotenemia, which may occur in this disease even when the amount of carotene in the diet is low. According to Escamilla, the conversion of carotene to vitamin A in the liver is hindered by the depressing effect of the lowered metabolism and tends to improve gradually under treatment with thyroid substance. Escamilla also mentions the opinion held by Stepp and Wendt that the thyroid hormone is antagonistic to vitamin A and governs the rate of its consumption. In hyperthyroidism the consumption is accelerated and the rate of change from carotene to vitamin A is increased, with resultant low serum carotene, whereas in hypothyroidism the opposite is found, the vitamin A in the serum remaining normal or low whereas the carotene is increased. Carotenemia was likewise noted in a case of Simmonds's disease, probably due to a similar mechanism of lowered metabolism.[38] Edwards and his co-workers[41] using spectrophotometric analysis of skin color, found an excess of carotene in the skin of castrate and eunuchoid men, which reverted to normal on treatment with testosterone propionate.

A therapeutic curiosity has been reported by Bendes,[42] who put carotenemia to a practical use. Blond tuberculous children were fed vegetables in abundance. The resultant carotenoid pigmentation of the skin protected them from blistering during heliotherapy and facilitated tanning of the skin.

Carotenemia may be present in liver disease owing to failure of that organ to convert the provitamin carotene to vitamin A, but may be readily masked by the accompanying jaundice. The three-layer test of Greene and Blackford[21] allows the laboratory demonstration of excess carotene in the serum even though excess bilirubin is also present.

Being a fat-soluble substance, carotene is poorly absorbed in obstructive jaundice and sprue.[43] Likewise, the presence of mineral oil in the gastrointestinal tract interferes with the absorption of carotene.[44] Hyperthyroidism can lower blood carotene.[38] Under such circumstances the blood-carotene level may be less than normal. Similarly low blood-carotene levels may result when the food intake of carotene is low. Such conditions may contribute to vitamin A deficiency, especially when preformed vitamin A is not present in adequate amounts. Little if any attention has been paid to the skin color when the blood and tissue caro-

tene is less than normal. Such changes are probably of no clinical significance as regards skin color, but are undoubtedly significant in relation to the production of vitamin A deficiency.

Carotenemia has been experimentally produced many times in human beings by excess consumption of carotene-rich foods.[21] Determination of the time required to produce carotenoderma under clinical circumstances has been difficult to evaluate for obvious reasons. Almond and Logan[24] state that 4 pounds of excess carrots per week for seven months are necessary. Wood and Agnor[45] mention a patient who ate two carrots daily for a year. Rosen's[46] patient weekly ate two bunches of carrots for a year. I have seen one clinic patient with carotenemia who had a history of eating pumpkin or squash pie daily for several months. A youth of twenty with carotenoderma seen at an army induction station had eaten several large carrots daily for about seven months. Some time previously he had read that carrots improved aviator's vision for night flying. He had eaten the carrots in anticipation of making a "good showing" in the eye tests when he applied for the Army Air Corps. All these statements refer to items additive to an average diet. A perusal of the dietary history of recorded cases reveals that a wide variety of foods, taken in variable amounts for a varying duration, have been responsible. In general, the time has been one of months rather than of weeks. These factors and varying individual susceptibility make it difficult to predict how much pigmented food a normal person must eat to develop a significant degree of carotenemia.

Children are said to develop carotenemia more readily than do adults. Hess and Myers[20] produced carotenemia in infants by feeding two oranges, an egg, or 2 ounces of spinach daily for a month. They noted, as have others since, an individual variation in susceptibility to the accumulation of carotenoid pigments in the blood.

Of special interest in Almond and Logan's[24] paper is the infant who developed carotenoderma after only two months on the breast milk of its carotenemic mother. Pariente, Present and Ralli[26] mention that De Buys reported the case of a carotene-pigmented baby born to a carotenemic mother, the child remaining yellow until weaned.[26] The carotene pigment is present in breast milk, whereas bilirubin is usually not.

Almond and Logan[24] in England report their observations on 4 women who showed such a pronounced carotene pigmentation of the skin that a tentative diagnosis of hemolytic anemia, pernicious anemia or obstructive jaundice was at first considered. In each case excessive amounts of carrots had been consumed, these evidently being a common dietary item in England at present. Their report emphasizes once more the ease with which carotenemia may be confused with jaundice. This is the main reason why every physician should be familiar with the clinical picture of carotenemia and the specific features that distinguish it from jaundice.

The eating habits of a nation change with war. Rationing in this country will result in the consumption of more fresh vegetables and less meat, butter, cheese and so forth. It is possible that carotenemia may become more prevalent in the United States than in the past. It is a condition worth considering in the differential diagnosis of any obscure, long-standing case of mild jaundice.

Excess carotene is in part excreted in the sweat and reabsorbed by the horny layer of the skin.[24] Characteristically the yellow pigmentation is noticeable first and predominantly in the nasolabial folds and over the forehead, where sebaceous glands abound, and in the palms and soles, where the horny layer of the skin is the thickest.[21–24] According to a case reported by Gandy,[30] "in the palms and soles the tinting was deepest on the outer edges, a classical feature." A lighter degree of accentuation of pigmentation may be noted in the upper eyelids, the inner canthi, the ears, the anterior folds of the axillas and over areas subject to pressure, such as the elbows, knees and malleoli.[30] This uneven distribution of the lipochrome pigment in the skin of persons with carotenemia is more noticeable than variations in distribution of bilirubin pigment in the skin of jaundiced patients. When the carotenemia is long-standing and severe, the rest of the body skin may become pigmented.

Many patients have mild degrees of carotenemia without a detectable carotenoderma. The blood-carotene threshold necessary to produce visible carotenoderma is not clear. In one experiment Pariente and his co-workers[26] noted carotenoderma when the blood-carotene level reached 0.54 mg. per 100 cc., whereas it was 0.50 mg. for 3 diabetic patients with carotenoderma. Stueck, Flaum and Ralli[34] noted clinical carotenoderma in each of 13 diabetic patients with serum-carotene levels varying from 0.21 to 0.8 mg. per 100 cc. and averaging 0.39 mg. They mention the average normal serum value as 0.11 mg. This suggests that carotenoderma may be noted when the serum-carotene level reaches two to five times the normal value.

The yellow color of carotenemia has been variously described as canary, lemon, ocher or golden,[21] canary yellow being perhaps the commonest term used. It never manifests the bronze, orange, saffron or green tint of jaundice. The serum in carotenemia is described as yellowish to orange.[21]

The mucous membranes and particularly the scleras are not stained by carotene; the latter re-

main white, in contrast to the early and marked presence of bilirubin in this area in true jaundice. Subconjunctival or submucosal fat, if present, may be stained, however, and lead to confusion. Attention must be paid to this clinical minutia if one wishes to use the appearance of the scleras or mucous membrane as a differential point. A paper by Wise and Diasio[29] contains four remarkable full-page colored plates showing the appearance of the face, palms, soles and serum of a patient with carotenemia. A perusal of these plates will be worth while for anyone not familiar with this clinical picture.

Carotene causes no feeling of ill-health except the anxiety occasioned by the skin discoloration; this is particularly true if an erroneous diagnosis is made to explain the "jaundice." Itching, so commonly present in jaundiced patients, is absent in carotenemia.

Carotenemia does not significantly change the color of the urine or of the stools. Almond and Logan[24] attempted extraction of the yellow color of the urine from their patients with petroleum ether, without success. The urine was said to have been deep orange in some of their patients.

The yellow color of the serum due to excess carotene may be confused with hyperbilirubinemia if the potassium dichromate color standards are used. The three-layer test of Greene and Blackford[21] enables the diagnosis of carotenemia to be made, even when excess bilirubin is present in the blood. Equal quantities of serum, alcohol and petroleum ether are shaken in a tube, and on standing separate into three layers; the top layer of petroleum ether contains the lipochrome pigments, the middle alcohol layer bears bilirubin, and the serum proteins are precipitated in the bottom layer.

The pertinent differences between carotenemia and jaundice are summarized in Table 1.

TABLE 1. *Differential Features of Carotenemia and Jaundice.*

DIFFERENTIAL FEATURES	CAROTENEMIA	JAUNDICE
Pigment responsible for the yellow color	Carotenoid (lipochrome) pigments	Bilirubin
Areas where pigmentation is first noticed	Forehead, nasolabial folds, palms, soles and over pressure areas	Scleras, mucous membrane under tongue, and body areas with thin skin
Extent of pigmentation when of severe degree	Entire skin with accentuation in areas mentioned above	Entire skin, scleras and mucous membranes; least on palms and soles.
Scleras	Free of pigment	Pigmented
Mucous membranes	Usually free of pigment	Pigmented
Color of pigment	Canary or lemon yellow	Yellow with green, bronze, orange or saffron tint
Urine	No significant color change	Except for "retention" jaundice, dark from presence of bilirubin
Stool	No change	Clay-colored in obstructive jaundice; normal or darker in other types of jaundice.
Icteric index (potassium dichromate standards)	Increased	Increased
Blood bilirubin (quantitative van den Bergh test)	Normal	Increased
Greene and Blackford's three-layer test	Lipochrome yellow pigments in top petroleum ether fraction	Yellow bilirubin pigment in center alcohol layer
Dietary history	Excess ingestion of foods rich in carotenoid pigments	Generally not significant as an etiologic background
Diseases accentuating or responsible for its production	Diabetes mellitus, kidney failure, myxedema, liver disease and possibly other endocrine disorders	Except for liver disease, other diseases responsible for carotenemia do not as a rule cause jaundice
Itching of skin	Not present	Frequent
Effect on health	No effect on health	Almost always a serious condition
Duration	Lasts as long as foods rich in lipochromes are consumed in excessive amounts (weeks to months or more)	Varies with type of jaundice
Time required to produce disease	Several months of excess ingestion of foods rich in lipochrome pigments	Days to weeks
Transmitted by breast milk to nursing child	Yes	No

PHRYNODERMA

Vitamin A deficiency in man results in impaired dark adaptation of the eyes (night blindness), dryness of the cornea and conjunctivas (xerosis, or xerophthalmia when severe) and a characteristic skin change (phrynoderma), as well as certain systemic changes.

Most patients are unaware of their night blindness, its detection being possible only by means of a dark-adaptation test. As a rule it responds rapidly (within days) to vitamin A therapy. Severe xerophthalmia is rare in this country. Mild xerosis is common; it may be symptomless and not readily

detected clinically. It usually responds well to therapy.

The specific cutaneous lesions considered characteristic of vitamin A deficiency were first recognized and described in 1931 by Frazier and Hu[47] in China. Their observations have been amply confirmed, and many descriptions of similar lesions seen in this country are now on record.[48–53]

The early change is one of simple dryness (xeroderma).[48, 53] When more severe, according to Markowitz,[54] the normal skin epithelium atrophies and is replaced by proliferating basal cells that become keratinized. A similar process in the skin glands and ducts causes accumulation of keratinized epithelium, which by protruding from the pilosebaceous follicular orifices results in the hyperkeratotic papules (hyperkeratosis follicularis) so characteristic of this disorder. Sebaceous-gland and sweat-gland function is diminished. The papule is commonly 1 or 2 mm. in diameter, but may in severe cases be as large as 5 mm.[53] It gives the skin a rough, grater-like feel, detected more easily by palpation than by inspection when mild, but readily noticeable if severe. The follicular papules are most prominent on the neck, back, buttocks, calves, elbows, knees and the posterolateral aspects of the upper arms and thighs. Dryness of the scalp is common. The lesions when present on the face resemble acne but are not pustular[48]; they are not frequent in this location.

The skin may become quite pigmented, a finding common in Negroes and Asiatics[55] but evidently a rarity in the white race.[56] Itching may occur[53] and at times be extremely severe.[57] There may be loss of hair in the severely involved areas. A gaping hole is left if a papule is pulled out of a follicle. Broken-off hairs or coiled, unerupted hair may be contained in the papule. This papular eruption has been called "goose-skin" because of its resemblance to cutis anserina ("goose pimples"), produced by reflex contraction of the erector pilorum muscles. The term "phrynoderma" (meaning "toad skin") introduced by Nicholls[58] is most descriptive of the dermal manifestations of severe avitaminosis A and already has wide usage. Markowitz[54] refers to it as "Frazier and Hu disease." However, a more appropriate eponym, if one is to be used, is "the Frazier and Hu syndrome," since follicular hyperkeratosis also occurs in scurvy. Keratosis pilaris of the dermatologic literature and its synonyms, lichen pilaris, lichen spinulosum, ichthyosis follicularis and so forth, are believed to be descriptive terms for the cutaneous manifestations of phrynoderma.[53]

Frazier and Hu[59] believed that avitaminosis A may produce only a xerosis of the skin in infants and children, the characteristic follicular keratosis rarely occurring before sexual maturity. Lehman and Rapaport[53] point out that this impression, although widely held, needs revision, and on the basis of their own experience added to impressive support from the literature state that follicular lesions are not infrequently found among underprivileged children.

Lehman and Rapaport[53] studied the families of the children whom they noted to manifest phrynoderma, and were surprised at the frequency with which it occurred in other members of the families. This familial occurrence may have been due to the fact that all the families consumed a deficient diet. These authors remarked, however, that "some hereditary disturbance in vitamin A metabolism, interfering with the utilization of vitamin A, or producing an increased minimal requirement for this substance, may be considered also."

In contrast to the rapid improvement usually noted for night blindness, phrynoderma responds poorly to therapy, two to four months or longer of vigorous therapy being the usual requirement.[49, 60] Straumfjord[52] has noted some patients who, after four years of continuous oral therapy, showed only partial subsidence. The very chronicity of phrynoderma readily allows a person to be in and out of mild deficiency superimposed on the background of chronic skin changes never completely relieved. This probably accounts for the frequent inability to detect night blindness in what otherwise seems like a case of vitamin A deficiency. While working at an army induction center, I have been impressed by the frequency with which varying degrees of phrynoderma and even mild ichthyosis have been noted in a cross section of the young adult male population. On most occasions, questions relative to subjective night blindness were answered in the negative. A photometer test would have been required to detect the night blindness. Milder degrees of follicular hyperkeratosis are usually overlooked,[52] or else not treated vigorously enough or long enough to obtain a satisfactory therapeutic response.

The specificity of these lesions as indicative of avitaminosis rests on their frequent association in the same person with xerosis and impaired dark-adaptation, careful dietary histories of intake of vitamin A and response to vitamin A therapy. In addition, they have been produced in human beings kept on an experimental vitamin A-free diet.[61–63]

Keil[64] has reviewed the earlier literature contending that hyperkeratosis follicularis may also occur in scurvy. Typical of these papers is the one by Wikthire[65] published in 1919. These lesions

were commonly called "scorbutic goose flesh" and "lichen scorbuticus." The common criticism of this idea has been that these scurvy patients had an unrecognized accompanying vitamin A deficiency. The question appears definitely answered by the appearance of these lesions in Crandon[66] during his six-month period of self-induced pure scurvy. I had the opportunity to examine Crandon's hyperkeratotic follicular lesions, and noted them to resemble in every way those described in the literature on avitaminosis A. I was also able to compare them with similar ones that developed in a patient whom I had placed on an experimental vitamin A-free diet.[63] Crandon's skin became dry and slightly rough, and the hairs fragmented easily and often grew abnormally in the follicle, all of which are changes that are seen in vitamin A deficiency. Crandon's dark-adaptation test and his blood vitamin A level were both normal. Besides, he took 30,000 international units of vitamin A daily throughout the experiment. It thus appears evident that hyperkeratosis follicularis may be seen in both scurvy and avitaminosis A. Until the red perifollicular areola or perifollicular hemorrhages develop in scurvy they cannot be told apart—a differential point emphasized by Machella.[67]

The "shark-skin" appearance of the filiform excrudescences of inspissated sebum on the faces of pellagrins and riboflavin-deficient persons may also be confused with phrynoderma. However, the primary localization in the face, the seborrheic skin and the absence of the excrudescences on the extremities rule out phyrnoderma.

Field and his co-workers[68] have emphasized the frequency with which patches of hyperkeratosis appear over the pressure areas (elbows, knee, soles and so forth) in the type of chronic pellagra seen in the northern part of this country. Callus formation was also common. These changes responded to therapy specific for pellagra. Such areas of hyperkeratosis may be confused with some aspects of the phrynoderma of avitaminosis A.

Moore, Spies and Cooper[69] noted hyperkeratosis of the skin in the histologic study of skin specimens from pellagrins, and concluded that a dificiency in the vitamin B complex produced a disturbance in keratinization.

The pathogenesis of phrynoderma is not clear. Vitamin A is not present in the epidermis, even though this layer of the skin is especially sensitive to its deficiency.[54] Cornbleet and Popper,[70] utilizing a special fluorescence and microscopic technic, were able to demonstrate it only in the underlying fat cells. It did not appear in the epidermis, even with a high intake of vitamin A. Carotene is present in the epidermis[31]; supposedly, however, it cannot function locally without conversion to vitamin A.

The factors that determine the deposition, mobilization and distribution of vitamin A in the body are largely unknown.[52] Since vitamin A, unlike vitamins B and C, is not water-soluble, it cannot readily diffuse in tissue fluids. Since it is present in the blood, the adequacy of the blood supply to a given region may also determine the amount of vitamin A furnished, lesions being unlikely to develop where the blood supply is abundant and being of common occurrence in areas with decreased circulation. Straumfjord[52] uses the aforementioned premises to explain the characteristic distribution of the follicular hyperkeratosis on the back, elbows, buttocks, calves and the posterolateral aspect of the thighs and arms. He points out that these are the body surfaces on which the weight of the body rests during sleep and sitting, and that the resultant mechanical pressure of the body weight diminishes the blood flow and therefore the supply of vitamin A to the areas involved, with resultant localization there of the lesions. Straumfjord[52] believes that corns and callosities may in some cases represent a localized dyskeratotic epidermal change due to a similar pressure mechanism. He reports that in some of his patients taking 100,000 international units of vitamin A daily for long periods (several months to three years) the disappearance of corns and callosities was observed even though present in the same skin areas for many years before treatment was commenced. Whether ingested arsenic that is deposited in the skin may not combine with vitamin A carried there by the blood, thus explaining the follicular hyperkeratosis and palmar and plantar keratoses that develop in certain persons following the administration of arsenicals is another query raised by this worker.

Keratosis Follicularis (Darier's Disease)

The standard textbooks on dermatology describe Darier's disease as an obscure chronic skin disorder, commoner in males than in females, commencing early in life, at times demonstrating a familial tendency,[71] and characterized at first by discrete, firm, keratotic follicular papules of the same color as the skin. With time the papules become darker, turning red and then brownish or purplish, coalesce, and form papillomatous masses. The eruption is symmetrical and widespread. The palms and soles become horny and thickened. Although the skin disorder is chronic and usually intractable to treatment, the general health remains unimpaired.

The resemblance of this disease to the skin manifestations described for avitaminosis A have not gone unnoticed. Peck, Chargin and Sobotka[72] present convincing evidence linking the pathogenesis of this disorder to some abnormality of vitamin A metabolism. They studied in detail 4 patients with Darier's disease, not only utilizing the clinical responses to vitamin A therapy but also following the blood vitamin A and carotene levels, and in 2 cases the dark-adaptation curves as well. They showed clearly that night blindness occurs in patients with Darier's disease. The eruption in 3 cases improved when massive vitamin A therapy was given orally over a considerable period. In all 4 cases the patients, while on a diet that contained a normal amount of vitamin A, showed a decided decrease in the vitamin A content of the blood serum even though the blood carotene level was normal. This suggested that there might have been a hereditary weakness in vitamin A absorption or in conversion of provitamin A (carotene) to vitamin A. Massive doses of vitamin A given orally raised the blood vitamin A to normal, but it became low again when this therapy was discontinued. Curiously enough, massive intramuscular doses seemed to lower the blood vitamin A level.[73] Peck[73] mentioned later that excessive vitamin A intake (over 300,000 international units) might make the keratotic papules become bullous. Welton's[74] observations of a patient confirm in general the findings of Peck and his co-workers with regard to the blood findings of the carotene and vitamin A blood levels.

There are now on record the results obtained by various physicians who have treated Darier's disease with massive doses of vitamins.[75–82] These supportive data, given in Table 2, emphasize the magnitude of the vitamin dosage used and the duration of the time over which it must be administered. On the whole the results have been favorable and seem to support the belief that Darier's disease represents a disorder attributable to an abnormal metabolism of vitamin A. Inheritance of Darier's disease may represent inheritance of this metabolic abnormality. It should be emphasized that the skin usually improved but did not become entirely normal. This suggests that there may be other factors in the pathogenesis of Darier's disease in addition to impaired vitamin A metabolism.

TABLE 2. *Results of Treatment of Keratosis Follicularis (Darier's Disease) with Vitamin A.*

AUTHOR	PATIENT AGE	PATIENT SEX	DAILY *U.S.P.* UNITS OF VITAMIN A ORALLY	DURATION OF TREATMENT	EFFECT ON SKIN LESIONS
	yr.				
Welton[74]	29	F	80,000–300,000, finally kept on 200,000	About 1 yr.	Definite softening and increased pliability of skin; definite subjective improvement.
Newman[75]	19	F	150,000–25,000	5 wk.	Almost complete involution of the eruption
Barwasser[76]	38	M	200,000	4 mo.	Disappeared from legs; rest of body greatly improved.
Michelson[77]	26	M	25,000–240,000	5 mo.	Improvement
Sweitzer[78]	82	M	100,000	2 mo.	Decided improvement
Peck[79]	27	M	200,000–250,000 orally, also 100,000 intramuscularly	9 mo. 2 mo.	Decided involution, with relapse during the summer months
Michelson[80]	25	F	320,000–250,000	2 mo.	Much improvement
Abramowitz[81]	30	F	190,000	4 mo.	Considerable regression except on palms and soles
Hayne[82]	41	M	100,000	1 mo.	Definite improvement

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

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CASE 29211

PRESENTATION OF CASE

A fifty-three-year-old housewife was referred to the hospital because of a generalized skin rash and marked oliguria.

Approximately three months prior to admission the patient noticed a fissure at the tip of the right ala of the nose. Her physician prescribed sulfathiazole ointment, which she applied for several days every two or three weeks during which time the lesion temporarily healed, only to recur. Eleven days before entry her physician prescribed sulfathiazole by mouth, of which she took 4.5 gm. in thirty-six hours without improvement. The sulfathiazole was then increased to 1 gm. every four hours for the succeeding twenty-four hours, following which a generalized skin eruption developed. At that time her temperature rose to 102°F. and redness and swelling developed about the eyes. The drug was discontinued and the patient was admitted to a community hospital. There the patient received 2 gm. of sulfathiazole as a test dose. This was followed in several hours by an exacerbation of the skin eruption and a rise in the temperature to 104°F. During the three days prior to admission she vomited several times, and two days before entry the urinary output was found to be 10 cc. per day. No sulfonamide crystalluria was known to have occurred.

The past history showed that the patient had always been well. Five months prior to admission she had an attack of "acute asthma." The cardiovascular history was not remarkable, except that she had had nocturia (once) for five years. One son was frequently troubled with "hives."

Physical examination disclosed an obese, confused woman who seemed quite ill. The breath was not acidotic. Involving the face, neck, upper trunk and lower legs, was a rash that, in its earliest form, was dull, erythematous and maculopapular, with central nodules. Some of the lesions seemed to be hemorrhagic blebs; others were pustular and crusted. There was dullness at the bases of both lungs posteriorly, and fine crackling rales were audible as high as the scapulas. The heart was normal. The abdominal panniculus was very heavy. No abdominal masses were felt, and there was no costovertebral angle tenderness.

The blood pressure was 130 systolic, 64 diastolic. The temperature was 102°F., the pulse 110, and the respirations 21.

Examination of the blood revealed a hemoglobin of 14.3 gm., and a white-cell count of 27,200, with 95 per cent neutrophils, 3 per cent lymphocytes and 2 per cent monocytes. The red-cell count and platelets were normal. The urine was cloudy orange and acid, and gave a + test for albumin; the sediment contained many white cells and granular casts, 10 red cells and 13 epithelial cells per high-power field, and a great deal of amorphous debris, no crystals being seen. The nonprotein nitrogen was 64 mg. per 100 cc., and the chloride 76.3 milliequiv. per liter. The blood sulfathiazole was 2.2 mg. per 100 cc. Cultures of the skin lesions were negative.

A chest roentgenogram revealed areas of atelectasis in the lower lung fields. There was no gross consolidation. The heart appeared prominent in the region of the left ventricle, and the aorta was slightly tortuous.

Irregular fever continued for four days, but was subsequently normal. The pulse was usually 80 to 90 during hospitalization. Daily infusions of 1500 cc. of glucose in distilled water were given. The nonprotein nitrogen gradually rose; the patient felt nauseated and seemed somewhat disoriented. On the fifth hospital day the skin seemed improved. The nonprotein nitrogen was 99 mg. per 100 cc. The carbon dioxide combining power was 21 millimols and the chloride 71.9 milliequiv. per liter. The patient seemed short of breath but examination of the lungs was not remarkable. The white-cell count was 12,500. The daily urine specimen totaled 30 cc., was acid, had a specific gravity of 1.010 and showed a ++ test for albumin and a light-green sugar test; a test for diacetic acid was negative. The sediment contained 15 red cells, 40 white cells, 10 round cells and 6 epithelial cells per high-power field; no crystals were seen. Examination of the nose and throat on the sixth day revealed a subacute nasal pharyngitis. After removing thick, mucopurulent, stringy material, approximately 15 cc. of thin, frankly purulent material was aspirated from the nasopharynx. The mucous membrane was inflamed throughout. Oral hygiene was extremely poor, with large, dry, brown crusts throughout. On the sixth hospital day the nonprotein nitrogen was 144 mg. per 100 cc.; the chloride was 65 milliequiv., and the carbon dioxide combining power

*On leave of absence.

19.9 millimols per liter. The urine was alkaline in reaction, had a specific gravity of 1.020 and gave a +++ test for albumin. The sediment contained many white cells, red cells and round cells per high-power field.

The clinical state of the patient continued about the same. Through the first seven days in the hospital, she was quiet, worried about the lack of urine and yet complained but little. The skin cleared slowly, but showed dull erythema and crusting. The blood pressure was fairly constant, 130 to 140 systolic, and the pulse was about 88. Suddenly on the eighth hospital day she became irrational, and breathing became labored. About 6:00 p. m. she suddenly became cyanotic, perspired a great deal and appeared to be in shock. The blood pressure dropped to 50 systolic, and moist rales were present throughout the lungs. She did not respond to coramine and adrenalin, and died at 7:45 p.m. The nonprotein nitrogen was 136 mg. per 100 cc.

Differential Diagnosis

Dr. Wyman Richardson: A good after-dinner speaker once said that the way to give a good speech was to make copious notes, then forget and leave them at home. That is what I have done. I hope it comes out the same way, but I doubt it.

Before I forget it I want to point out that there was still sulfathiazole in the blood, 2.2 mg. per 100 cc. So far as I can figure, this was somewhere between three days and a week after she had had sulfonamide, but she still had a measurable amount in the blood.

I do not see how this can be interpreted in any other way than that this patient died of a sulfathiazole nephritis. Without going into the pathology of this condition, about which Dr. Mallory will tell you, it is my understanding that two things can occur. One is a deposition of crystals in the upper urinary tract, which may cause tubular blockage and a real sulfathiazole nephrosis. I also understand, from what Dr. Maisel[1] has observed, that there is another lesion, which involves the parenchyma of the kidney, and I think that this patient probably had that type of renal failure. But before getting involved in that, I think that I should mention the other possibilities.

There is the question whether this patient had an acute infection, perhaps streptococcal in type, followed by an acute glomerulonephritis; or whether she had some type of severe acute urinary infection with renal failure. So far as acute nephritis goes, the story does not seem to be very good for that. The cellular elements in the sediment were not conspicuous, and the whole picture does not seem to follow the course of an acute glomerulonephritis. On the other hand, an acute infection of the urinary tract in most cases runs a longer course than this.

If you consider, as I have, this picture to be due to sulfathiazole, and go back and add up the amounts of the drug given, the total is relatively small, about 12.5 gm. This seems a small amount to have produced a toxic damage to the kidney. However, this patient not only had an acute attack of asthma in the past but she had a child who had hives. The patient herself reacted to the drug with a definite febrile reaction and with a severe skin reaction. If she acted in that way there is no reason why the kidneys should not be affected.

A recent article — I have forgotten where it appeared — tends to minimize the severe reactions that this drug is capable of producing, on the basis that the drug is so useful that one can overlook the reactions, which on the whole are infrequent and rarely fatal. My reply is that death is 100 per cent fatal for any given patient, and I do not believe anyone has the right to treat benign conditions with a potentially toxic drug, thus running the risk of a fatal termination. And that leads up to the question of the treatment of the fissure about the tip of the ala with sulfathiazole ointment in a patient who is known to be allergic. Unless one believed that was a potentially dangerous lesion, which it could be if badly infected, one should not run the risk of sensitizing a person to a drug that may be a life-saving one later. I think it is probable that this patient was sensitized by the use of sulfathiazole ointment. The patient's physician decided to try sulfathiazole by mouth; since the patient had been sensitized, she developed a fever and then was sent to the hospital. There she was given a test dose of the drug.

That brings up another little sermon. If we are going to test someone for sensitivity to a drug, we do not want to use a large dose. In this case they used 2 gm. In the days when amidopyrin was being used and patients developed agranulocytosis, a test dose was given under carefully controlled conditions. The Scandinavian investigator Plum[2] did some experiments on amidopyrin sensitivity and found that some patients either died or came near dying from only 5 gr. of Pyramidon. If one is going to use a test dose, an extremely small amount should be given.

There is one other thing I should mention. I have been sensitized by Dr. Joseph Aub to Addison's disease, but one cannot explain this patient's picture on the basis of adrenal failure. Although she had a low blood-chloride level, there is no

mention about pigmentation and so forth, and it seems to me the whole story is that of renal, not adrenal, failure.

So I come down to a diagnosis of sulfathiazole nephritis with fatal termination.

DR. TRACY B. MALLORY: Conversations with my lay friends lead me to believe that many doctors now hand out tubes of sulfathiazole ointment and tell their patients to apply it every time they scratch their skin. I think it certainly is quite possible that any patient could be sensitized in that manner.

DR. JACOB LERMAN: How do you explain the low chloride, Dr. Richardson?

DR. RICHARDSON: On the basis of vomiting. I meant to mention that. I should have thought they would have given physiologic saline instead of distilled water.

DR. LERMAN: There is no mention of the blood-sodium level. She may have lost a lot of sodium by perspiration.

DR. RICHARDSON: That brought up in my mind the adrenal bugbear, but I think I shall throw it out.

CLINICAL DIAGNOSIS

Sulfonamide nephrosis.

DR. RICHARDSON'S DIAGNOSIS

Sulfathiazole nephritis.

ANATOMICAL DIAGNOSES

Sulfonamide interstitial nephritis, with granulomas.
Acute myocarditis.
Pulmonary edema.
Subacute and chronic pancreatitis.

PATHOLOGICAL DISCUSSION

DR. MALLORY: This case was tremendously important, and we had great difficulties in regard to post-mortem examination; Dr. Maisel eventually drove a hundred miles to perform the autopsy in an undertaker's parlor. It turned out to be worth while, since the kidneys are the most interesting we have seen.

The pair of kidneys weighed 650 gm., each kidney alone being the size of a normal pair of kidneys. The body had already been embalmed so we did not have a chance to see the kidneys in a fresh state. But even after embalming it was evident that they were markedly discolored, with very pale patches alternating with areas of hemorrhage. The change was most marked in the cortices, which were extremely swollen. The pelves showed no crystals, and even when the kidneys were examined under the dissecting microscope we could not find any crystals. Microscopic examination of the kidney showed an extreme degree of edema of the cortex and a very diffuse infiltration of lymphocytes, with a moderate number of plasma cells. There were so many inflammatory elements that at first glance one thought of pyelonephritis, but the infiltration was limited to the cortex and did not involve the pyramids. It was clear that the changes were not due to pyelonephritis. In addition to this diffuse infiltration there were small granulomas in the interstitial tissue, such as Maisel[1] has described in experimental cases of sulfonamide poisoning. I think I am correct in saying that he had not seen any case with the diffuse change that was present in this renal cortex. It is reminiscent of the entity that used to be called interstitial nephritis, which, in the period from 1895 to 1910, was a common finding in patients with scarlet fever, but which has almost completely disappeared as a disease at the present time, even in cases of scarlet fever.

The microscopic study also brought out other lesions of interest, which had not been apparent in the gross. There was a very severe and acute myocarditis, which has been described in sulfonamide reactions by French and Weller,[2] of Ann Arbor, but which we have never seen here. This was extensive enough so that I think the sudden terminal exitus was in part due to that as well as to the uremia. There was also an extensive change in the pancreas, but it is a little less certain whether one can blame it on the drug; very possibly it was of entirely different origin. A number of pancreatic ducts showed squamous-cell metaplasia, many of them blocked with inspissated casts. There was slight dilatation of the acini, as well as a moderate inflammatory infiltration and a few places where the islands of Langerhans were found imbedded in fat tissue without any surrounding acinar tissue, suggesting a significant degree of pancreatic atrophy; the picture is reminiscent of the very early stage of so-called "cystic disease of the pancreas" seen in small children.

Dr. Maisel, have you anything to add?

DR. BERNARD I. MAISEL: The only thing I should like to say is in answer to Dr. Richardson's comment that the blood level was 2.2 mg. per 100 cc. almost a week after the drug had been stopped. We have found that to be so when the kidneys are damaged. In other words, a diseased kidney often will not excrete the sulfonamide drugs; hence, if a patient who is given the usual dose of the sulfonamides develops a high blood level, one must suspect renal impairment and be extremely careful in continuing the drug.

DR. MALLORY: Dr. Nathaniel Faxon once remarked that he thought seriously of having tattooed upon his chest, "Do not give me any transfusions." I sometimes think it would be a good idea if one said, "Do not give me sulfonamide for any nonlethal complaint."

DR. GEORGE W. HOLMES: There is some evidence of lung pathology by x-ray. Did you find anything?

DR. MALLORY: There were pulmonary edema and epithelization of the alveoli, which suggest that the edema had been present for some time. This is not, however, the type of pulmonary edema that Dr. Schatzki has observed in nephritis.

A PHYSICIAN: Was the brain examined?

DR. MAISEL: No.

DR. WILLIAM B. BREED: This case brings up the question of the duty of the profession in educating or re-educating the public. I spend many of my waking hours preventing the promiscuous use of sulfonamides in patients because of the pressure brought to bear by friends, their families and themselves. We can do a great service if we, as physicians, will take this opportunity to continue the education of the public with respect to the use of these drugs, counteracting the influence of newspaper and magazine articles.

DR. RICHARDSON: We might start with the staff.

DR. BREED: That is one of the purposes of the above remarks.

DR. WILLIAM H. BECKMAN: Was there any evidence of periarteritis?

DR. MALLORY: No. There were a few cells around one coronary artery, but I do not think that makes it periarteritis.

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CASE 29212

PRESENTATION OF CASE

A fifty-eight-year-old housewife entered the hospital because of headaches of two weeks' duration.

Two weeks prior to admission, soon after a hearty supper, the patient suddenly became warm, dizzy and nauseated. She tried to vomit but could not. Approximately half an hour later she developed a sharp throbbing occipital headache and perspired profusely. She took bicarbonate of soda and promptly vomited, but without much relief. Because she felt weak and faint she went to bed. However, at no time did she lose consciousness. Her physician found the systolic blood pressure to be 185, and gave her codeine sulfate and "another tablet which lowered the blood pressure." During the two weeks prior to admission she had three similar attacks each lasting about half an hour, but these were not so severe and responded readily to "hypodermic injections." No auras accompanied these attacks, nor was a neurologic residual noticed afterward. There had been slight diminution of visual activity during the year prior to admission. The patient had no genitourinary symptoms.

The family history was noncontributory.

For more than twenty years the patient had had dizzy spells following "bilious attacks" from overeating. These occurred about every two years, were followed by nausea and vomiting and then spontaneously cleared. There had been no fever, chills or jaundice during these attacks. The patient had been married for thirty-six years, but had never been pregnant. A hysterectomy and bilateral salpingo-ophorectomy were performed eighteen years before admission for "fibroids of the uterus."

Physical examination disclosed a thin, nervous woman who seemed quite well. The heart was slightly enlarged to the left, and there was a short early blowing systolic murmur best heard in the aortic area. The lungs and abdomen were normal. A neurologic examination was not remarkable. The visual fields were normal.

The blood pressure was 140 systolic, 88 diastolic. The temperature, pulse and respirations were normal.

The examination of the blood revealed a red-cell count of 4,700,000, with a hemoglobin of 14.0 gm. and a white-cell count of 8800 with 58 per cent neutrophils. In eleven examinations of the urine the specific gravity varied from 1.010 to 1.018, was acid in reaction and gave a + test for albumin on two occasions; six times the sediment contained a few red cells, white cells and epithelial cells per high-power field. A blood Hinton test was negative. The nonprotein nitrogen was 32 mg. per 100 cc., and the blood sugar 92 mg. A phenolsulfonephthalein test showed 25 per cent excretion of the dye in the first fifteen minutes, and 60 per cent in two hours. The basal metabolic rate was +1 per cent. An electrocardiogram showed a normal rhythm, with a rate of 70. T_1 and T_2 were upright and of good amplitude, and T_3 was slightly inverted. There was a slight tendency to left-axis deviation. The P waves and the PR intervals were normal. An electroenceph-

alogram was said to have been consistent with a mild diffuse process resulting from hypertensive attacks.

On the third hospital day, at 9:00 p.m., a cold-pressor test was performed. The initial blood pressure was 115 systolic, 68 diastolic. After the left hand had been in ice water approximately forty-five seconds, the patient complained of excruciating bilateral occipital headache, radiating forward to the temples and to the forehead, and a severe pounding pain developed in these areas. This attack was identical with the spontaneous attacks. Five minutes later the blood pressure rose to 180 systolic, 110 diastolic. There was no palpitation, precordial pain, change in skin color, sweating, dizziness, nausea, blurring of vision, tinnitus or deafness. Within three minutes after the hand was removed from the water, the headache slowly began to disappear. However, the blood pressure continued elevated. There was little change in blood pressure when the head of the bed was elevated 15° or when the patient sat up. At the conclusion of the test, with the patient lying flat, the blood pressure was 178 systolic, 105 diastolic. At 10:30 p.m. the pressure was 134 systolic, 80 diastolic. Three hours later the patient had a typical attack, which began while she was in bed. Luminal had been administered approximately three hours prior to the attack. When seen, the patient was very restless, perspired freely, rolled about in bed complaining of a severe occipital headache and begged for sedation. The blood pressure was 174 systolic, 114 diastolic, and 170 systolic, 112 diastolic, in the right and left arms respectively with the patient flat in bed and the manometer level with the right arm. The pupils were small and did not react to light. There was questionable evidence of weakness of the left seventh cranial nerve. Ten minutes after morphine sedation the headache was relieved and the patient seemed quite comfortable.

An operation was performed on the eleventh hospital day.

Differential Diagnosis

Dr. Robert E. Glendy: In summary, this history is that of a woman in her sixth decade suffering from peculiar spells attended by a variety of symptoms and signs, among which was paroxysmal hypertension, and, who, after ten days of hospital observation, was thought to have a condition requiring operation. The problems are, Why did she need an operation and what was found at operation?

The past history is not remarkable except for bouts of indigestion attributed to overeating, which may very well have been due to this cause. These episodes went back over a period of twenty years, at intervals of about two years, and, at least in the patient's mind, bore no relation to the "spells" that finally brought her to the hospital. Whether the bilious spells were related to the present illness makes little difference in so far as the differential diagnosis is concerned, for we have no data concerning the blood pressure during the attacks of indigestion, and can only speculate about it. She was never pregnant, but I have no way of telling from the history whether this was by accident or design or for other reasons.

The attacks that began to occur two weeks prior to admission seem more complex and more incapacitating than anything that preceded them. They were characterized by flushing, dizziness and nausea, and later a throbbing occipital headache, profuse sweating, weakness and faintness. Induced vomiting did not afford much relief. One might encounter this set of symptoms under all sorts of circumstances, but the fact that they were attended by an elevated blood pressure should make one suspicious of a hypertensive crisis, even in the absence of the neurologic manifestations that so often occur in such crises. Subsequent observations failed to show a persistent hypertension. This is against hypertensive crisis as one usually thinks of it in individuals with well-advanced, often malignant hypertensive cardiorenal disease, when it is preceded by prodromes of malaise, headache, vomiting, apathy and paresthesias. There seems little doubt, however, that the attacks were on the basis of a sudden marked, paroxysmal rise in blood pressure without prodromal symptoms, and when the pressure returned to lower levels, the symptoms subsided. The only definite precipitating factor up to the time of admission seems to have been overeating; at least, other circumstances are not mentioned.

She is described on physical examination as thin and nervous, but seemed quite well. These statements are somewhat contradictory, but one can surmise from them that she was not of hypertensive habitus, that she was not cachectic and that she did not possess any of the bizarre physical manifestations of a glandular disorder. There was some cardiac enlargement, which I presume could be the result of even paroxysmal hypertension. If this presumption is correct, the systolic murmur heard in the aortic area might be explained on the basis of dilatation of the aortic ring. Furthermore, if the cardiac enlargement was the result of paroxysmal hypertension, this would indicate a condition of long-standing, slow progression, with acceleration during the few weeks before admission. There is certainly no con-

clusive evidence of a valvular lesion, such as aortic stenosis, but since this condition is sometimes attended by vertigo and fainting, one might consider it remotely as a factor in her symptoms and as a cause of the cardiac enlargement. I believe, however, that it can be discarded. No mention of the condition of the retinal arteries during or between attacks is made, so I shall assume that they were not remarkable.

"The pupils were small and did not react to light." I do not know how to interpret that finding. No mention is made of the pupils on initial examination. I presume that she had not had an opiate, although that is a possibility since she did get morphine later.

Do you know whether any ophthalmoscopic examination was made?

DR. REGINALD H. SMITHWICK: The pupils were normal.

DR. GLENDY: During the attack?

DR. SMITHWICK: No one looked during the attack. At the time of admission they were perfectly normal.

I happened to see this woman in an attack. She had several while in the hospital. One of these occurred when I suggested that she be operated on, — just as one occurred when her hand was put in ice water, — and it was a rather alarming attack. She was extremely nervous, had excruciating occipital pain, was restless and dizzy, with a definite elevation of the pulse rate, slight tremor, a feeling of constriction in the chest and a sense of impending disaster, — she thought that she was going to die, — and believed that she was going to have a severe nosebleed.

DR. GLENDY: That certainly gives a more complete picture of the attacks.

The initial blood-pressure reading of (140 systolic, 88 diastolic) is certainly within normal limits for the patient's age. Subsequent readings while at rest were even lower (115 systolic, 68 diastolic).

I can gather no light on the problem from the laboratory procedures. Two of eleven urines showed a + test for albumin, and in half the urine specimens there were a few red and white cells; but all tests of kidney function were normal. There was nothing clinically or by laboratory test to indicate disturbance of the basal or carbohydrate metabolism.

The results of the cold-pressor test were striking, demonstrating a sharp reactivity of the mechanism regulating the blood pressure. The response, however, was out of all proportion to what one might expect, even in patients with known persistent hypertension. I consider the cold as just another factor that reflexly precipitated the paroxysm of hypertension and its attendant symptoms.

There is only one condition I know of that might produce this clinical picture. It was referred to in 1934 by Belt and Powell[1] as the "suprarenal sympathetic syndrome" and occurs in patients with tumors arising from the chromaffin tissue. I believe this patient had such a tumor. Having chosen chromaffin-cell tumor (also called paraganglioma, pheochromocytoma and chromaffinoma) as the most likely diagnosis, there is little I can say against it. Two prominent features that have been present in most of the reported cases are precordial oppression and severe palpitation. This patient had no palpitation, but Dr. Smithwick did note that she experienced a sense of constriction in the chest. Loss of consciousness and convulsions do occur but are infrequent. The blood pressure is usually normal between attacks, as in this case, or may be persistently elevated, making the differential diagnosis between paraganglioma and late essential or malignant hypertension difficult. Palmer and Castleman[2] reported a case in which the patient had paroxysms of hypertension but also persistent hypertension between attacks. The mechanism involved in these attacks is thought to be the intermittent discharge of adrenaline into the blood stream from the site of the tumor. Crystalline adrenaline has been recovered from the tumors, which lends support to this idea, but on account of the extremely low concentrations of adrenaline in the blood even during attacks, it has not been possible, so far as I know, to isolate it from the blood stream. Is that a true statement, Dr. Albright?

DR. FULLER ALBRIGHT: Yes.

DR. GLENDY: The tumor may be located in either or both adrenal glands, or anywhere along the sympathetic chain where chromaffin cells exist, that is, as far down as the bifurcation of the aorta. Trauma or manipulation of the abdomen either in examination or in surgery may precipitate an attack. There is no evidence from the physical examination that any abdominal tumor exists in this case. In cases that have been reported, the use of contrast pyelography and pneumoperitoneum has been of value in localizing the adrenal tumors. Were any such studies done here?

DR. TRACY B. MALLORY: No.

DR. GLENDY: If I am forced to guess where the tumor lies, the following locations are most frequent in the order mentioned: right adrenal gland, left adrenal gland, bilaterally in the adrenal glands and, finally, the extramedullary chromaffin tissue, such as the sympathetic ganglions and the

carotid body. I shall guess on the law of averages that it is in the right adrenal gland.

The condition occurs predominantly in females in a ratio of 3:1, and most often in the third, fourth and fifth decades, but 1 case has been reported in an infant. Some of the reported cases have been confused with anxiety attacks or hysteria. Although there often is a marked rise in blood pressure in anxiety states, it is not of the magnitude encountered with the suprarenal sympathetic syndrome associated with a paraganglioma. Hyperthyroidism has also been confused with this syndrome, but the enlarged gland, other physical signs and elevated metabolic determinations usually make the distinction clear. The presence of hyperglycemia and glycosuria, which are sometimes found in cases of paraganglioma, has raised the question of diabetes mellitus, but the absence of a fundamental and continued disorder of sugar metabolism rules out this disease. Intermittent hypertension in association with cortical adrenal tumors has also been observed by Fishberg,[3] but his cases were accompanied by clinical manifestations of hirsutism and virilism not present in this case.

Dr. Mallory: Will you tell us your findings, Dr. Smithwick?

Dr. Smithwick: Paroxysmal hypertension is a rare disorder. In our experience here in the last ten years in studying hypertension of one sort or another we have seen only a very few cases. Up to within a year, a total of 116 cases associated with adrenal medullary tumors was reported in the literature.[4] The great majority of these tumors were discovered at autopsy. In addition there have been a few cases, I do not know how many, in which the patients had paroxysmal hypertension and at operation no adrenal tumors were found. As Dr. Glendy has said, the tumors occur most commonly in the adrenal glands or in their vicinity, but occasionally they are found in other parts of the body, and the fact that most of the operations that have been done have been limited to exploration of the adrenal glands does not prove that a paraganglioma might not have existed elsewhere. However, there are occasional cases of paroxysmal hypertension of a neurogenic type not associated with adrenal tumors, and that is what this particular case proved to be.

The patient was explored carefully from the low lumbar to the midthoracic level on both sides by the retroperitoneal extrapleural approach, and both adrenal glands were found to be normal. Biopsy specimens were taken from both adrenal glands and from both kidneys. The main renal arteries were normal.

Because of the similarity between the patient's reflex blood-pressure response to emotion and cold and those of the usual patient with essential hypertension, the chief difference being the duration of the attacks, it seemed best, in the absence of a pheochromocytoma, to denervate the splanchnic bed. This was done, and the attacks have not recurred in the year and a quarter since operation. It therefore appears that this patient had paroxysmal hypertension of neurogenic origin.

Clinical Diagnosis

Paroxysmal hypertension.

Dr. Glendy's Diagnosis

Chromaffin-cell tumor (paraganglioma), probably of right adrenal gland.

Anatomical Diagnosis

(Paroxysmal hypertension of neurogenic origin.)

Pathological Discussion

Dr. Benjamin Castleman: The adrenal and renal biopsies were normal. Careful examination of the renal arterioles showed no vascular disease. This woman falls in the group of hypertensive patients recently reported[5] in which study of the renal biopsy specimens, taken when sympathectomy was performed, showed little or no arteriolar disease, which is evidence in favor of the theory that the hypertensive state antedates the renal vascular disease.

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CONCENTRATED HUMAN SERUM ALBUMIN

Every physician, no matter what his interest or specialty, should know how to treat certain medical emergencies. One of the most important of these is shock, an everyday occurrence in the armed forces overseas, but a sufficiently frequent condition in civilian practice to demand preparedness on the part of every practitioner. The necessity for this is emphasized by the possibility of air raids and the actuality of disasters like the Cocoanut Grove fire. Recent improvements in the methods of preparing and preserving blood plasma and the development of blood banks have placed potent weapons against shock in the hands of the medical profession. In order to use these weapons intelligently, it is necessary to understand the differences between the various forms of preserved plasma and its derivatives. Much valuable practical information about the available blood substitutes appears in a paper by Newhouser and Lozner, published elsewhere in this issue of the *Journal*. The authors speak authoritatively from their experience in the Blood Research Division of the National Naval Medical Center, and include information about concentrated human serum albumin, the latest addition to the group of blood replacement fluids used in the Army and Navy.

All previous methods of plasma preservation have been aimed at keeping the plasma intact. The work of Cohn[1] and his colleagues has introduced a radically new idea into this field, namely, the separation of plasma into its active components and their use in a relatively pure state for specific purposes. Concentrated human serum albumin, one of the accepted remedies for the treatment of shock, represents the fulfillment of this idea, and is an example of how a practical achievement can arise from scientific work carried out on a fundamental level.

Concentrated human serum albumin was developed for the armed services as a result of the need in certain situations for a blood substitute that would take up a minimum of space and be ready for use with a minimum of preparation. Although dried plasma has become the basic therapeutic agent in the Army and Navy, it requires a bulky package and a certain amount of time is necessary to reconstitute the plasma for use. Albumin, as issued to the armed forces,[2] is in solution, ready for instant injection, and is concentrated to such an extent that it occupies little space.

Albumin has certain properties that make this possible. It is not only the most stable protein of the plasma but also the most soluble; hence it can be concentrated to form solutions that are capable of withstanding considerable extremes of temperature without deterioration. It has been used sufficiently to indicate that, when properly prepared, reactions almost never occur. It is well

known that the colloidal osmotic pressure of the blood plasma is due to its proteins and that, of these proteins, albumin is responsible for at least 80 per cent of the colloidal osmotic pressure, although it constitutes only slightly over half the total protein. Hence, it is the most effective component of the plasma in restoring the depleted plasma volume characteristic of surgical shock.

Proof of the practical usefulness of concentrated albumin has been supplied in a study by Woodruff and Gibson,[3] in which it was found to be an effective agent in the treatment of traumatic shock in civilian hospitals in the United States. That albumin is an exceedingly safe remedy is the inevitable conclusion from the paucity of reactions observed. That it may lead to trouble if used in excessive dosage without an understanding of its particular properties is reasonable, and is emphasized by Newhouser and Lozner. However, the precautions to be observed in its use are mainly those that apply to the use of plasma itself. If huge doses of albumin are used, three difficulties may arise. First, the patient may develop a deficiency of the globulin components of the plasma, among which are to be found the antibodies, which assist in the defense against infection, and prothrombin and fibrinogen, which are essential constituents of the blood-clotting mechanism. In the second place, the osmotic potency of albumin is so high that the circulation may be overloaded. This is hardly a danger in the treatment of shock, in which the patient is suffering from a deficiency of circulating blood. The third possible difficulty results from the fact that albumin is put up in concentrated solution. This means that, as the concentrated protein solution is injected into the blood stream, fluid is drawn into the circulation from the patient's tissues. If the patient is extremely dehydrated, with the interstitial fluid reserves markedly depleted, concentrated albumin can scarcely be expected to produce as good results as in a well-hydrated one, and treatment in such patients should be supplemented with oral or parenteral fluids.

It should be emphasized that, just as plasma is not a "blood substitute" but a therapeutic agent in its own right, so albumin is not just a "plasma substitute" but a therapeutic agent with new properties and specific indications. Concentrated plasma or serum differs from it, because the concentration of the globulins leads to high viscosity, whereas the viscosity of the official 25 per cent albumin solution is no greater than that of whole blood, as Newhouser and Lozner point out. The concentration of electrolytes is much higher in concentrated plasma than in concentrated albumin.

The effectiveness of this new remedy under military conditions remains to be tested on the field of battle. There is ample proof from preliminary trials in civilian hospitals that concentrated human serum albumin is not only a safe but an exceedingly valuable agent for the emergency treatment of shock because of its instant availability and its rapid action in increasing the blood volume. The concept of utilizing one component of plasma for a specific indication may have many other fruitful applications to the treatment of disease.

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THE ROCKEFELLER FOUNDATION REPORTS

Gearing its work to the war emergency, yet maintaining its long-range viewpoint, the Rockefeller Foundation in 1942 appropriated $8,227,867, distributed for the most part in the major fields of public health, the medical, natural and social sciences, the humanities and reconstruction in China. The two largest items were $2,700,000 for public health and $1,434,000 for the medical sciences. Seven members of the staff of the International Health Division were absorbed into the armed forces to deal with such specialized problems as malaria and typhus, and twelve are serving

part time on Washington committees and commissions in connection with the medical problems of the Army and Navy. A similar disposal was made of the staff serving abroad.

In the yellow-fever campaign, the Foundation's experts studied the problem of incidental jaundice resulting from yellow-fever vaccine. The vaccine is now being successfully made without the causative component, but a further investigation of jaundice has grown out of this interest. In Africa, field investigation revealed a high prevalence of *Aedes aegypti*, the common carrier of yellow fever, and mass vaccination of the population was undertaken.

In malaria, the chief problem is now to develop a new drug not subject to the limitations of quinine and its substitutes — the military and public-health value of such a discovery is obvious. In 1942 the Foundation's laboratory carried on this search in co-operation with the Department of Chemistry of Harvard University. Another problem engaging the Foundation's attention is elimination of the mosquito *Anopheles gambiae* from Africa. In India, the Foundation's experts disclosed that a systematic spraying technic was remarkably effective in interrupting the transmission of malaria.

The 1940 appropriation of $100,000 for scholarships for British medical students in this country was repeated last year. Fifty of these students are attending various medical schools in this country and Canada, and they have expressed cordial appreciation of the benefits thus received.

The Foundation's aid to psychiatry is of special significance in view of the global war. In 1942 more than half the money it spent in the medical service was devoted to this special field. A total of $495,410 was given for the further development of psychiatry centers in nine institutions, including the medical schools of Yale, Harvard and the University of Tennessee.

The relations of the Foundation with Iceland, begun in 1927 with a survey of the medical school in Reykjavik, have been continued. Last year $15,000 was appropriated to the University of Iceland for student laboratory work. In addition, a grant was made to the university to provide internships in the United States for four of the medical school's graduates.

Research in the biological sciences was aided in England, Sweden and Switzerland, — the three countries where opportunities for support are still open, — with grants totaling $60,410. In the United States a grant in genetics was made to Professor George W. Beadle at Stanford University, and two in physiology to Princeton and the University of Minnesota.

The detailed appropriations in the medical sciences are far too numerous to be listed here. Those of special interest to New England include a grant of $48,000 to Harvard University for teaching and research in psychiatry, and one of $114,000 to the same university for research in epilepsy over a six-year period. A grant of $15,000 was allotted to the Judge Baker Guidance Center in Boston for a children's psychiatric consultation center on a day-nursery and residential plan.

MEDICAL EPONYM

Walcher's Position

This was described by Gustav Adolph Walcher (b. 1856), of Stuttgart, in a brief article entitled "Die Conjugata eines engen Beckens ist keine konstante Grösse, sondern lässt sich durch die Körperhaltung der Trägerin verändern [The Conjugate of a Contracted Pelvis Is Not a Fixed Measurement, but Varies with the Position of the Woman's Body]," in *Centralblatt für Gynäkologie* (13: 892, 1889). A portion of the translation follows:

> If a woman well advanced in pregnancy (my observations were made almost entirely in such) whose pelvis is contracted in the conjugate diameter, be placed on the examining table with the upper part of the body moderately elevated and the knees held as close as possible to the body, the promontory is most easily reached: the diagonal conjugate measures, for example:
>
> F. (26-year-old para I) 10.2 cm.
> B. (40-year-old para II) 10.3 cm.
> S. (36-year-old para IV) 10.2 cm.
>
> If a pillow is placed under the sacrum and the legs are allowed to hang down over the end of the table as far as possible, the promontory may be felt to re-

cede with the lowering of the knees. The diagonal conjugate now measures:

F. 11.1 cm. (a difference of 9 mm.)
B. 11.6 cm. (a difference of 13 mm.)
S. 11.0 cm. (a difference of 8 mm.)

R. W. B.

WAR ACTIVITIES

INDUSTRIAL HEALTH

The following recommendations concerning a control program for venereal disease in industry have recently been made by the Advisory Committee on the Control of Venereal Diseases, United States Department of Public Health.

* * *

In order to assemble current authoritative information and to formulate basic principles applicable to a program of venereal-disease control in industry, the Surgeon General has appointed an advisory committee to the United States Public Health Service. This committee has outlined the objectives of such a program as follows:

A. *Medical and Public Health*:

(1) To find and refer for proper medical management all cases of venereal diseases among workers in industry.

(2) To establish equitable policies for the employment of applicants and continuation of services of employees who have venereal diseases.

(3) To co-ordinate the community and industrial venereal-disease control programs.

B. *Employee*:

(1) To improve the physical condition of employees.

(2) To reduce the number of workdays lost through illness or injury.

(3) To provide job placement.

(4) To prolong and increase the earning power of employees.

C. *Employer*:

(1) To reduce compensation costs.

(2) To lessen work interruptions and labor turnover.

(3) To enhance production by increasing the efficiency of workers.

(4) To minimize personnel problems.

In order to assure agreement on all phases of fundamental policy, the committee recommends that certain agencies be consulted in carrying out this program: the labor department, industrial commission or similar department of state government; the appropriate committee of the state medical society; the association representing employers; the labor organizations; and the appropriate voluntary health and welfare associations.

Responsibility for the administration of the program should be shared by the industrial-hygiene and venereal-disease divisions of the state health department. The program should not be inaugurated without a complete educational program. The employee should be convinced that adequate treatment protects both his health and his ability to earn a living, and the employer that not all cases of venereal disease are infectious, through an educational program before venereal-disease control measures are introduced.

In order that the control program may be effective, pre-employment examinations should be mandatory for all workers. Laboratory tests for syphilis and gonorrhea should be made a part of the periodic, re-employment or "return from illness" physical examinations that are the policy of the industry. The interval between examinations should under no circumstances be more than three years.

It is of utmost importance that the results of the medical examination be considered confidential between the worker and the medical staff. Information should be furnished to others only with the consent of the individual concerned or, failing this, on legal advice. The medical staff should make proper recommendations to the management concerning the physical fitness of the employee for work. When the usual clinical record is kept in an open file, venereal-disease forms should be filed in the medical departments for the use of the medical staff only.

There is no reason for denying employment to an applicant or for discharging an employee because an examination has revealed evidence of syphilis or gonorrhea, provided:

(1) That the employee agrees to place himself under competent medical management.

(2) That, if the disease is in the infectious stage, employment should be delayed or interrupted until such time as a noninfectious state is established through treatment and open lesions are healed.

(3) That when syphilis exists in a latent stage, employment should not be delayed or interrupted.

(4) That employment may be deferred or denied when the individual is an industrial hazard.

(5) That occupational readjustments of employees be made of individuals developing disabling manifestations.

(6) That workers with syphilis in any of its stages be excluded from areas where there is exposure to chemicals that may produce toxic reactions, and that those having cardiovascular syphilis or neurosyphilis should not be exposed to physiologic stresses.

(7) That workers with gonorrhea should be allowed to work only under special medical observation during the administration of sulfonamide drugs.

The applicant or the employee whose examination reveals evidence of a venereal disease should be called to the industrial physician's office for a conference. He should be instructed concerning the nature of the disease in order that he may co-operate intelligently with the requirements of the program. He should be referred to a reputable source for medical attention and be furnished with a letter directed to his physician stating the results of the examination and what is expected of the employee in regularity of treatment if he is to be employed. The industrial physician should receive a record of treatment at about monthly intervals. The names of persons who have neglected or refused treatment should be turned over to the health department for appropriate action in bringing them to treatment.

The plant physician making a tentative diagnosis of communicable syphilis or gonorrhea should without delay acquaint the appropriate health authority with the facts.

CORRESPONDENCE

OLD MEDICAL DICTIONARIES WANTED

To the Editor: Although the chief function of the Citizens Committee for the Army and Navy, Incorporated,

is to furnish dayrooms in camps and to supply recreational equipment to the Army, Navy and Coast Guard, we also strive to fill unusual requests received from special-service officers. In many cases, the materials or services requested are theoretically covered by Army and Navy appropriations. As a practical matter, red tape and endless delays substantially negate the right of various units to benefit from governmental appropriations.

Typical examples are the urgent requests that have been made to us from a number of units for medical dictionaries. We are advised that many trainees are wholly unfamiliar with the medical terms that they are obliged to use in their training. This puts an additional burden on their instructors.

This committee has appealed to various medical libraries and schools without success. If you would generously grant us space in your columns to publish this letter, we have great hopes that some of your medical readers will be willing to send to Committee Headquarters, 13 Commonwealth Avenue, Boston, any medical dictionaries, no matter how old or how dilapidated, that they can spare. If the dictionaries cannot be sent or delivered to Committee Headquarters, arrangements can probably be made by telephone (COMmonwealth 6810) to have them picked up.

JOHN HEARD, *Vice-President*
The Citizens Committee for the Army and Navy, Incorporated

13 Commonwealth Avenue
Boston

WILLIAM ALLAN

To the Editor: It is particularly appropriate to memorialize in the *Journal* the life and works of William Allan of Charlotte, North Carolina, who recently died of pneumonia in Winston-Salem, whither he had gone not long ago to take a new post at the Bowman–Gray Medical School in the field of inheritance of diseases in which he was a pioneer.

Dr. Allan was not only one of the leading physicians and internists in the United States and an authority and intensive worker in his chosen special field, but he had become known personally, through his associations during World War I, to a group of New Englanders who made up the large portion of Base Hospital Unit No. 6, stationed at Talence near Bordeaux, France, from 1917 to 1919. As the chief internist of Unit O attached to the hospital in the winter of 1918, he quickly endeared himself to the Yankees in Talence and also quickly demonstrated his great ability both in the theory and in the practice of medicine.

Many of us in New England, both in and out of that old hospital unit, have continued to keep in touch with Bill Allan ever since. He was a man whom all his friends loved dearly. One of the interesting circumstances of his life was that his father was one of Stonewall Jackson's most important officers in the War between the States. His grandfather founded and taught at the Military Institute of Virginia.

Medicine, and especially the new field of hereditary medicine, will miss Dr. Allan, but his friends and associates will miss him still more.

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BOOK REVIEW

Spontaneous and Experimental Leukaemia in Animals. By Julius Engelbreth-Holm, M.D., director of the Cancer Research Laboratory, Danish Anti-Cancer League, and chief pathologist of the Finsen Institute and Radium Station, Copenhagen. 8°, cloth, 245 pp., with 44 illustrations and 3 tables. Edinburgh: Oliver and Boyd, 1942. 15 shillings.

This book, which was written at the behest of the famous Lady Tata Memorial Trust by an internationally known investigator with a broad clinical experience and viewpoint, gathers up the many diverse and often tangled threads of leukemia as seen both in spontaneous and experimental animal leukemia and in man. It thus fills a long-felt need for both the interested clinician and the investigator.

Of the spontaneous and transmissible leukemias in fowl and mammals, the lymphogenous type is by far the most frequent, and in fowl appears to have a seasonal variation. Plasma-cell leukemia and its related multiple myelomatosis is unknown in animals. Although mouse leukemia can be transmitted by a single cell, but never by a cell-free filtrate, there are inferential facts that a virus etiology may be a factor. In fowl, myelogenous — but not lymphogenous — leukemia and erythroleukemia can be produced by a filterable virus. The spontaneous remission and recovery of fowl leukemia are discussed. A virus has been found in fowl sarcomas of the same histologic type as mammalian sarcomas.

The role of heredity and its significance in spontaneous and transmitted animal leukemias are discussed, together with the present knowledge relative to experimentally produced leukemias in fowl and mammals by carcinogenic agents, x-ray irradiation and estrogenic substances.

Of greatest interest to clinicians is the final chapter, which deals with the nature of animal leukemias and their relation to human types. All the evidence points to the conclusion that leukemia is a neoplastic proliferation. Although, in contrast to other neoplasms, leukemia is generalized from the start, this probably depends on the peculiarity of the blood-forming tissues themselves, which are normally scattered throughout the body and not situated in a simple locus. Furthermore, they produce cells that lack the ability to form cohesive tissue and thus, in proliferating, produce a generalized disease, usually without nodal metastases. The many relations between such diseases are pointed out, for example those between lymphosarcoma and lymphatic leukemia. Thus the peculiarities that distinguish leukemia from other tumors can be readily explained as consequences of the special features normally characterizing the hematopoietic tissues. Direct evidence concerning the neoplastic nature of leukemia has been developed by the author and Furst, who worked with mixed leukemia-sarcoma strains. As Engelbreth-Holm states, leukemia research has become a link in general tumor research, and results in this field will presumably be of value in the understanding of the others. He adds, "There can be no legitimate grounds for doubt that leukemia in animals, especially in mice, is the same disease as that in man . . . with the solution of the problem of human leukemia as the final goal. . . ."

This book, which presents an authoritative analysis of all the scattered notions and studies of animal and human leukemia, is a "must" on the list of those interested in tumors and blood diseases.

(Notices on page viii)